BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

(19) Europäisches Patentamt
Eur pean Patent Offic
Office européen des brevets

(11) Publication number: **0 280 771 B1**

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **28.07.93**

(51) Int. Cl.5: **C07D 487/04**, C07D 207/12, C07D 403/12, C07D 417/12, C07D 401/12, A61K 31/40, //C07F7/18,(C07D487/04, 209:00,205:00)

(21) Application number: **87117021.3**

(22) Date of filing: **18.11.87**

The file contains technical information submitted after the application was filed and not included in this specification

(54) 3-Pyrrolidinylthio-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid derivatives and processes for the preparation thereof.

(30) Priority: **24.11.86 GB 8628063**
31.12.86 GB 8631081
21.04.87 GB 8709399
17.07.87 GB 8716937

(43) Date of publication of application:
07.09.88 Bulletin 88/36

(45) Publication of the grant of the patent:
28.07.93 Bulletin 93/30

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(56) References cited:
EP-A- 0 072 710
EP-A- 0 182 213
EP-A- 0 243 686

ANGEWANDTE CHEMIE, Int. Ed. Engl., vol. 24, 1985, pp. 180-202

(73) Proprietor: **FUJISAWA PHARMACEUTICAL CO., LTD.**
3, Doshomachi 4-chome Higashi-ku
Osaka-shi Osaka 541(JP)

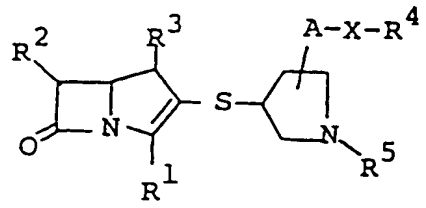
(72) Inventor: **Murata, Masayoshi**
No. 7-17, Higashitokiwadai 7-chome Toyono-cho
Toyono-gun Osaka(JP)
Inventor: **Tsutsumi, Hideo**
No. 16-3-301, Yuhigaoka 2-chome
Toyonaka-shi Osaka(JP)
Inventor: **Matsuda, Keiji**
No. 14-18, Kosobecho 3-chome
Takatsuki-shi Osaka(JP)
Inventor: **Hattori, Kohji**
No. 694, Otoriminamimachi 5-chome
Sakai-shi Osaka(JP)
Inventor: **Nakajima, Takashi**
No. 17-10, Shinsenrikitamachi 1-chome
Toyonaka-shi Osaka(JP)

EP 0 280 771 B1

(74) Representative: **Türk, Gille, Hrabal, Leifert**
Brucknerstrasse 20
W-4000 Düsseldorf 13 (DE)

Description

The present invention relates to novel 3-pyrrolidinylthio-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid derivatives and pharmaceutically acceptable salts thereof; mor particularly, it relates to novel 3-pyrrolidinylthio-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid derivatives of general formula



(I)

wherein R^1 to R^5, A and X are as defined below and pharmaceutically acceptable salts thereof, which are highly active against a number of pathogenic microorganisms and therefor useful as antimicrobial agents, to processes and intermediate compounds for the preparation thereof, to a pharmaceutical composition comprising the same as an active ingredient, and to the use of the same as a medicament and in the treatment of infectious diseases caused by pathogenic microorganisms in human being or animals.

3-Pyrrolidinylthio-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylic acid derivatives having a structure similar to the above formula (I) are already known from EP-A-0 072 710 and EP-A-0 182 213. The essential structural difference between the compounds disclosed in the above publications and those of the present application is the nature of the substituent in the pyrrolidine ring (A-X-R^4 in the above general formula) and in X which is not aquivalent to X-R^4, respectively.

Furthermore, in EP-A-0 243 686 which is a publication according to Article 54.3 EPC, similar compounds are disclosed which differ from the compounds of the present invention in the nature of the Y substituent which is not the same as X-R^4 in the above formula (I).

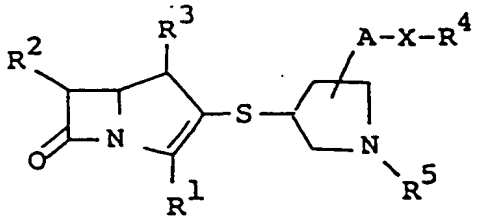
All these compounds disclosed in the above publications are known to have an antimicrobial activity. The antimicrobial properties of these compounds and their derivatives are well-documented and numerous modifications have been made to the basic skeleton whilst still retaining their qualitative activity (see for example "Angew. Chem. Ind. Ed. Engl.", 24 (1985), pages 180-202).

In the applicant's co-pending EP-A-0 272 456 3-pyrrolidinylthio-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylic acid derivatives are described which differ from the compounds of the present invention in that R^4 is protected or unprotected ureido(C_1-C_6)alkyl when X is oxygen.

The object of the present invention is to provide further novel 3-pyrrolidinylthio-1-azabicyclo [3.2.0]hept-2-ene-2-carboxylic acid derivatives which have unexpected advantages over the compounds already known from EP-A-0 072 710 and EP-A-0 182 213 mentioned above.

According to the present invention this object can be achieved by providing novel 3-pyrrolidinylthio-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid derivatives having general formula (I) following below.

According to a first aspect the present invention relates to novel 3-pyrrolidinylthio-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxyylic acid derivatives which can be represented by the following general formula:



(I)

in which

R^1 is carboxy or protected carboxy,

R^2 is hydroxy (C_1-C_4)alkyl or protected hydroxy (C_1-C_4)alkyl,

R^3 is hydrogen or C_1-C_6 alkyl,

R^4 is protected or unprotected hydroxy (C_1-C_6)alkyl; protected or unprotected hydroxy (C_1-C_6)alkyl having protected or unprotected amino; halo (C_1-C_6)alkyl; protected or unprotected carbamoyl-(C_1-C_6)alkyl; protected or unprotected amino (C_1-C_6)alkyl; protected or unprotected ureido (C_1-C_6)alkyl; protected or unprotected ureidocarbonyl (C_1-C_6)alkyl; triazolyl(C_1-C_6)alkyl; saturated or unsaturated 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), or containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), wherein said heterocyclic group may be substituted by suitable substituent(s) selected from C_1-C_6 alkyl, amino, amino(C_1-C_6)-alkyl, mono(or di) (C_1-C_6)alkylamino, mono(or di) (C_1-C_6)alkylamino(C_1-C_6)alkyl and imino-protective group; or C_1-C_6 alkylsulfonyl;

R^5 is hydrogen, C_1-C_6 alkanimidoyl or imino-protective group,

A is C_1-C_4 alkylene, and

X is sulfur, oxygen, imino or protected imino,

provided that

when X is oxygen,

then R^4 is not "protected or unprotected ureido(C_1-C_6)alkyl",

and pharmaceutically acceptable salts thereof.

The 3-pyrrolidinylthio-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid derivatives and their pharmaceutically acceptable salts of the present invention have an antimicrobial activity, i.e. they are highly active against a number of pathogenic microorganisms and are useful as antimicrobial agents. Therefore, they can be used as a medicament and in the treatment of infectious diseasis caused by pathogenic microorganisms in human being or animals.

Preferred compounds of the present invention are those of the above general formula (I), wherein

R^2 is hydroxy(C_1-C_4)alkyl,

R^3 is hydrogen or C_1-C_4 alkyl,

R^4 is carbamoyloxy(C_1-C_4)alkyl; [phenyl(or nitrophenyl)(C_1-C_4)alkoxy]carbonyloxy(C_1-C_4)alkyl; [triphenyl(C_1-C_4)alkoxy](C_1-C_4)alkyl; [tri(C_1-C_4)alkylsilyl]oxy(C_1-C_4)alkyl; hydroxy(C_1-C_4)alkyl; hydroxy(C_1-C_4)alkyl having amino or phenyl(or nitrophenyl)(C_1-C_4)alkoxycarbonylamino; dihalo-(C_1-C_4)alkyl; carbamoyl(C_1-C_4)alkyl; trihalo(C_1-C_4)alkanoylcarbamoyl(C_1-C_4)alkyl; N-[bis{(C_1-C_4)alkoxyphenyl}(C_1-C_4)alkyl]carbamoyl(C_1-C_4)alkyl; halosulfonylcarbamoyl(C_1-C_4)alkyl; amino-(C_1-C_4)alkyl; N-[phenyl(or nitrophenyl)(C_1-C_4)alkoxycarbonyl]amino(C_1-C_4)alkyl; (C_1-C_4)-alkylsulfonylamino(C_1-C_4)alkyl; ureido(C_1-C_4)alkyl; phenyl(C_1-C_4)alkylureido(C_1-C_4)alkyl; ureidocarbonyl(C_1-C_4)alkyl; phenyl(C_1-C_4)alkylureidocarbonyl(C_1-C_4)alkyl; triazolyl(C_1-C_4)alkyl; saturated or unsaturated 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), or containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), which may have C_1-C_4 alkyl, N,N-di(C_1-C_4)alkylamino(C_1-C_4)alkyl or phenyl(or nitrophenyl)(C_1-C_4)alkoxycarbonyl; or (C_1-C_4) alkylsulfonyl;

R^5 is hydrogen or C_1-C_4 alkanimidoyl, and

A is C_1-C_4 alkylene;

in particular those wherein

R^3 is C_1-C_4 alkyl, and

R^4 is carbamoyloxy(C_1-C_4)alkyl; hydroxy(C_1-C_4)alkyl; hydroxy(C_1-C_4)alkyl having amino or nitrophenyl(C_1-C_4)alkoxycarbonylamino; difluoro(C_1-C_4)alkyl; carbamoyl(C_1-C_4)alkyl; amino(C_1-C_4)alkyl; N-[nitrophenyl(C_1-C_4)alkoxycarbonylamino(C_1-C_4)alkyl; (C_1-C_4)alkylsulfonylamino(C_1-C_4)alkyl; ureido(C_1-C_4)alkyl; ureidocarbonyl(C_1-C_4)alkyl; triazolyl(C_1-C_4)alkyl;, tetrazolyl, pyrrolidinyl, thiadiazolyl or tetrazolyl, wherein said heterocyclic groups may have C_1-C_4 alkyl, N,N-di(C_1-C_4)alkylamino(C_1-C_4)alkyl or nitrophenyl(C_1-C_4)alkoxycarbonyl; or (C_1-C_4)alkylsulfonyl;

especially those wherein

R^2 is 1-hydroxyethyl,

R^3 is methyl,

R^4 is 2-hydroxyethyl, 2-carbamoyloxyethyl, 3-amino-2-hydroxypropyl,difluoromethyl, carbamoylmethyl, 1-carbamoyl-1-methylethyl, 2-aminoethyl, 2-amino-1,1-dimethylethyl, 2-(methylsulfonylamino)ethyl, 2-ureidoethyl, 1-1-dimethyl-2-ureidoethyl, ureidocarbonylmethyl, 1,2,4-triazolylmethyl, pyrrolidinyl, thiadiazolyl, 1-methyl-1H-tetrazolyl, 1-[2-(N,N-dimethylamino)-ethyl]-1H-tetrazolyl or methylsulfonyl,

A is methylene, and

X is sulfur, oxygen or imino.

A particularly preferred compound is

(4R,5S,6S)-3-[(2S,4S)-2-{(2-ureidoethyl)thiomethyl}pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-

oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid.

According to a further preferred embodiment the present invention relates to compounds of general formula (I) wherein

R^4 is 2-hydroxyethyl, 2-carbamoyloxyethyl, carbamoylmethyl, 1-carbamoyl-1-methylethyl, 2-aminoethyl or 2-(methylsulfonylamino)ethyl, and

X is oxygen;

in particular to the compound

(4R,5S,6S)-3-[(2S,4S)-2-(2-aminoethyloxymethyl)pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid acetate;

especially those compounds wherein

R^4 is 2-ureidoethyl or methylsulfonyl, and

X is imino.

A particularly preferred compound of the invention is

(4R,5S,6S)-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-3-[(2S,4S)-2-{(2-ureidoethyl)aminomethyl}pyrrolidin-4-yl]-thio-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid.

According to another preferred embodiment the present invention relates to compounds of the above formula (I), wherein R^3 is hydrogen;

in particular those, wherein

R^4 is unsaturated 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s);

especially those compounds, wherein

R^2 is 1-hydroxyethyl,

R^4 is pyridyl,

R^5 is hydrogen,

A is methylene, and

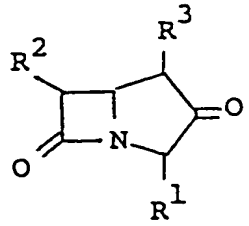
X is sulfur.

A further particularly preferred compound of the present invention is

(5R,6S)-6-[(1R)-1-hydroxyethyl]-7-oxo-3-[2S,4S)-2-(pyridin-4-ylthiomethyl)pyrrolidin-4-ylthio]-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylic acid.

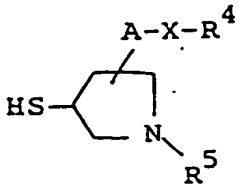
According to a second aspect the present invention relates to a process for the preparation of the compounds of general formula (I) as defined above and salts thereof, which comprises

(a) reacting a compound of the formula :



(II)

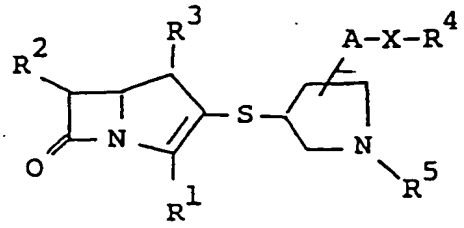
wherein R^1, R^2 and R^3 are each as defined above, or a reactive derivative at the oxo group thereof or salts thereof with a compound of the formula :



(III)

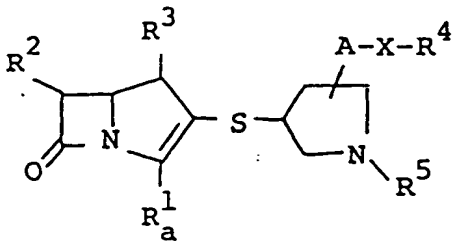
wherein R^4, R^5, A and X are each as defined above,

or salts thereof to give a compound of the formula :



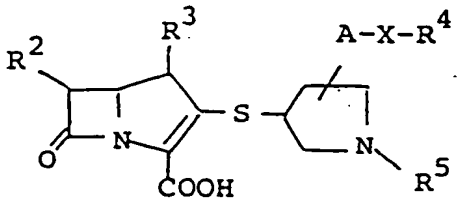
(I)

wherein R^1, R^2, R^3, R^4, R^5, A and X are each as defined above,
or salts thereof; and
(b) subjecting a compound of the formula :



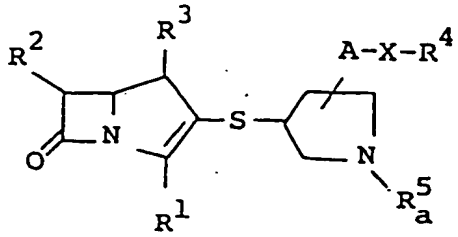
(Ia)

wherein R^2, R^3, R^4, R^5, A and X are each as defined above, and
R_a^1 is protected carboxy,
or salts thereof to elimination reaction of the carboxy-protective group on R_a^1 to give a compound of the formula :



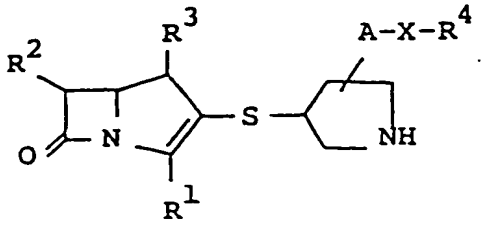
(Ib)

wherein R^2, R^3, R^4, R^5, A and X are each as defined above,
or salts thereof; and
(c) subjecting a compound of the formula :



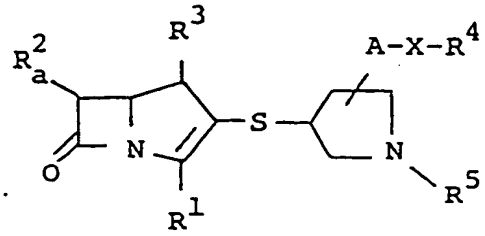
(Ic)

wherein R^1 R^2 R^3, R^4, A and X are each as defined above, and
R_a^5 is imino-protective group,
or salts thereof to elimination reaction of the imino-protectiv group of R_a^5 to give a compound of the formula :



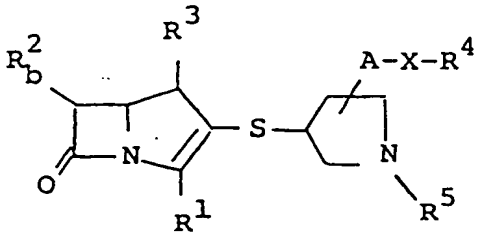
(Id)

wherein R^1, R^2, R^3, R^4, A and X are each as defined above,
or salts thereof;
and
(d) subjecting a compound of the formula :



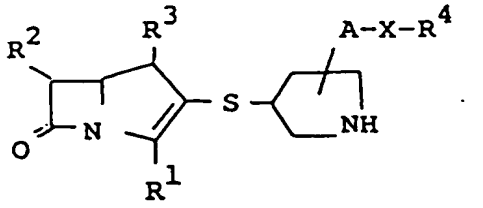
(Ie)

wherein R^1, R^3, R^4, R^5, A and X are each as defined above, and
R_a^2 is protected hydroxy(C_1-C_6)alkyl,
or salts thereof to elimination reaction of the hydroxy-protective group on R_a^2 to give a compound of the formula :



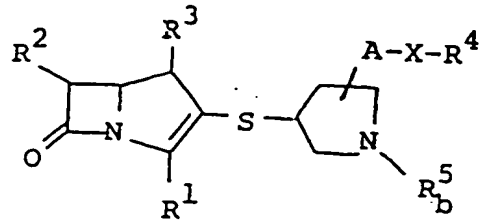
(If)

wherein R^1, R^3, R^4, R^5, A and X are each as defined above, and
R_b^2 is hydroxy(C_1-C_6)alkyl,
or salts thereof;
and
(e) reacting a compound of the formula :



(Id)

wherein R^1, R^2, R^3, R^4, A and X are each as defined above,
or salts thereof with C_1-C_6 alkanimidoylating agent to give a compound of the formula :



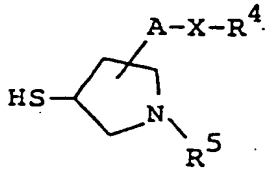
(Ig)

wherein R^1, R^2, R^3, R^4, A and X are each as defined above, and
R^5_b is C_1-C_6 alkanimidoyl,
or salts thereof.

According to a third aspect the present invention relates to a pharmaceutical composition comprising as an active ingredient a compound of formula (I) as defined above in admixture with a pharmaceutically acceptable carrier or excipient.

According to a fourth aspect the present invention relates to the use of the compound of the above formula (I) as a medicament and in particular for use in the treatment of infectious diseases.

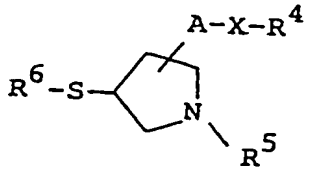
According to a fifth aspect the present invention relates to a compound of general formula:



(III)

in which R^4, R^5, A and X are each as defined above or salts thereof.

According to a sixth aspect the present invention relates to a process for the preparation of the compound of general formula (III) or salts thereof which comprises subjecting a compound of general formula:



(IIIa)

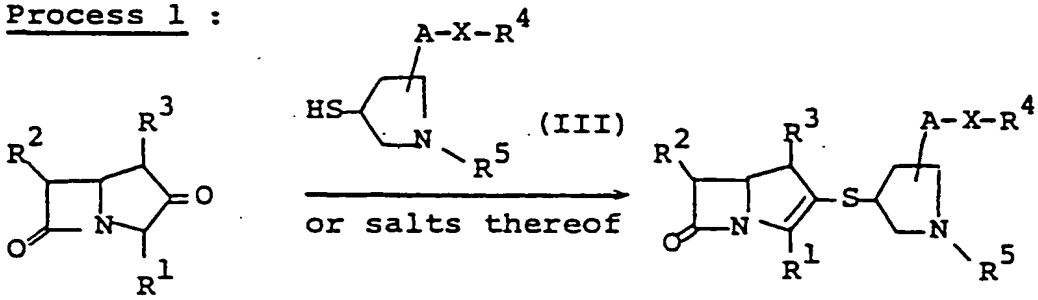
in which R^4, R^5, A and X are each as defined above, and
R^6 is mercapto-protective group,
or salts thereof to elimination reaction of the mercapto-protective group of R^6.

In the object derivatives of formula (I) and the intermediate compounds of formula (III), it is to be understood that there may be one or more stereo-isomeric pair(s) such as optical isomers due to asymmetric carbon atom(s), and such isomers are also included within the scope of the present invention.

Suitable pharmaceutically acceptable salts of the object derivatives (I) are conventional non-toxic salts and may include a salt with a base such as an inorganic base salt, for example, an alkali metal salt (e.g. sodium salt and potassium salt), an alkaline earth metal salt (e.g. calcium salt and magnesium salt), an ammonium salt, an organic base salt, for example, an organic amine salt (e.g. triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt and dibenzylamine salt; a salt with an acid such as an inorganic acid addition salt (e.g. hydrochloride, hydrobromide, sulfate, and phosphate), an organic acid addition salt (e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, and toluenesulfonate); a salt with a basic or acidic amino acid (e.g. arginine, aspartic acid, and glutamic acid; and an intermolecular quaternary salt.

According to the present invention, the object derivatives (I)' and pharmaceutically acceptable salts thereof can b prepared by the processes as illustrated by the following reaction schemes.

Process 1 :



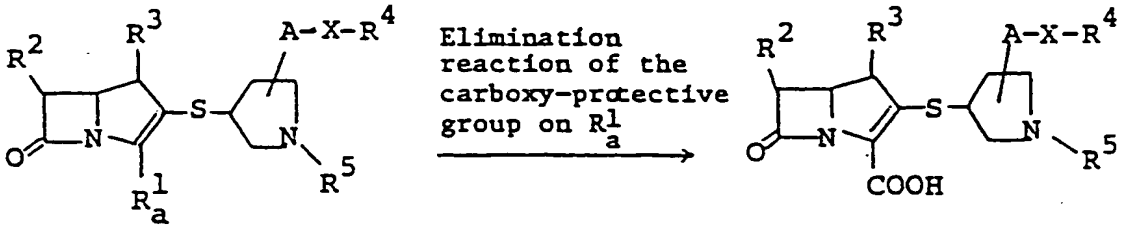
(II)

or a reactive derivative at the oxo group thereof or salts thereof

(I)

or salts thereof

Process 2 :



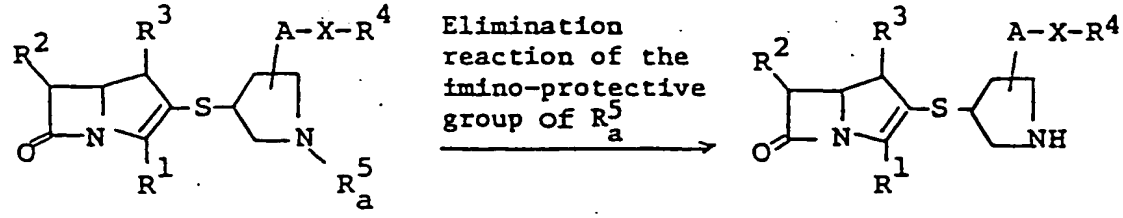
(I-a)

or salts thereof

(I-b)

or salts thereof

Process 3 :



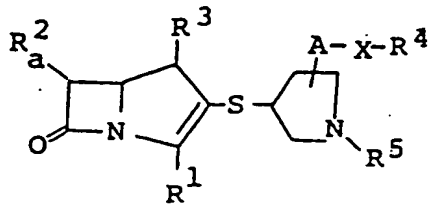
(I-c)

or salts thereof

(I-d)

or salts thereof

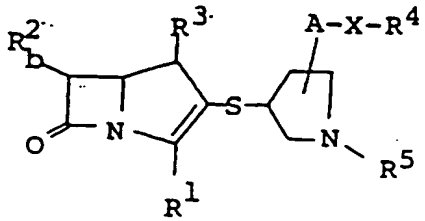
Process 4 :



(I-e)

or salts thereof

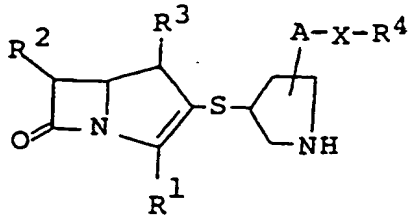
Elimination Reaction of the hydroxy-protective group on R^2_a



(I-f)

or salts thereof

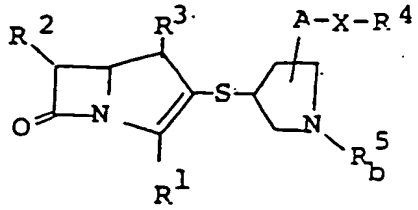
Process 5 :



(I-d)

or salts thereof

C_1-C_6-Alkanimidoylating Agent



(I-g)

or salts thereof

in which R^1, R^2, R^3, R^4, R^5, A and X are each as defined above,

R^1_a is protected carboxy,

R^2_a is protected hydroxy (C_1-C_6)alkyl,

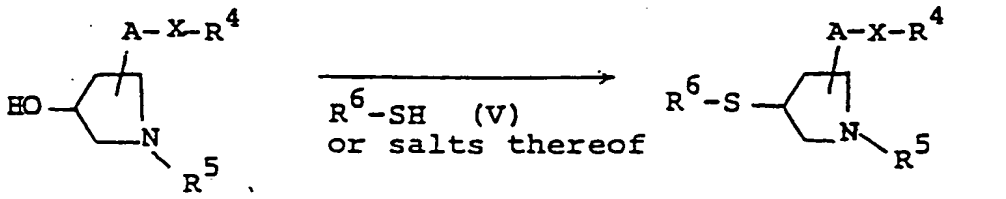
R^2_b is hydroxy(C_1-C_6)alkyl,

R^5_a is imino-protective group, and

R^5_b is C_1-C_6- alkanimidoyl.

The compound (III) used in the Process 1 is new and can be prepared, for example, by the following methods or a conventional manner.

Method A :

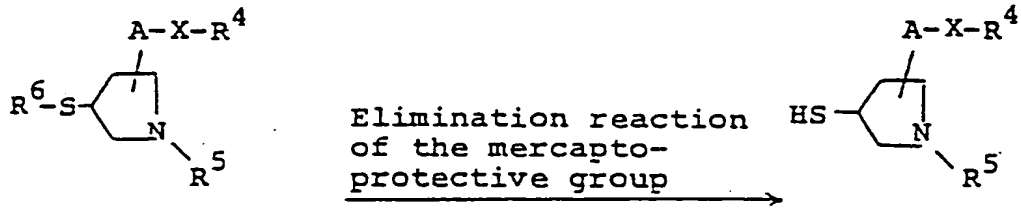


(IV) (III-a)

or a reactive derivative at the hydroxy group thereof or salts thereof

or salts thereof

Method B :



(III-a) (III)

or salts thereof or salts thereof

in which R^4, R^5, A and X are each as defined above, and

R^6 is a mercapto-protective group.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention includes within the scope thereof are explained in detail as follows.

Suitable "protected carboxy" may include esterified carboxy wherein "esterified carboxy" can be referred to the ones as mentioned below.

Suitable examples of the ester moiety of an esterified carboxy nay be the ones such as C_1-C_6- alkyl ester (e.g. methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester, and hexyl ester) which may have at least one suitable substituent(s), for example, C_1-C_6-alkanoyloxy(C_1-C_6)alkyl ester [e.g. acetoxymethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester, hexanoyloxymethyl ester, 1-(or 2-)acetoxyethyl ester, 1-(or 2- or 3-)acetoxypropyl ester, 1-(or 2- or 3- or 4-)acetoxybutyl ester, 1-(or 2-)propionyloxyethyl ester, 1-(or 2- or 3-)propionyloxypropyl ester, 1-(or 2-)butyryloxyethyl ester, 1-(or 2-)isobutyryloxyethyl ester, 1-(or 2-)pivaloyloxyethyl ester, 1-(or 2-)hexanoyloxyethyl ester, isobutyryloxymethyl ester, 2-ethylbutyryloxymethyl ester, 3,3-dimethylbutyryloxymethyl ester, and 1-(or 2-)pentanoyloxyethyl ester], C_1-C_6-alkanesulfonyl(C_1-C_6)alkyl ester (e.g. 2-mesylethyl ester), mono(or di or tri)halo(C_1-C_6)alkyl ester (e.g. 2-iodoethyl ester, and 2,2,2-trichloroethyl ester), C_1-C_6- alkoxycarbonyloxy(C_1-C_6)alkyl ester (e.g. methoxycarbonyloxymethyl ester, ethoxycarbonyloxymethyl ester, propoxycarbonyloxymethyl ester, t-butoxycarbonyloxymethyl ester, 2-methoxycarbonyloxyethyl ester, 1-ethoxycarbonyloxyethyl ester, and 1-isopropoxycarbonyloxyethyl ester), phthalidylidene(C_1-C_6)alkyl ester, or (5- C_1-C_6-alkyl-2-oxo-1,3-dioxol-4-yl) (C_1-C_6)alkyl ester [e.g. (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-ethyl-2-oxo-1,3-dioxol-4-yl)methyl ester, and (5-propyl-2-oxo-1,3-dioxol-4-yl)ethyl ester]; C_1-C_6-alkenyl ester (e.g. vinyl ester, and allyl ester); C_1-C_6-alkynyl ester (e.g. ethynyl ester, and propynyl ester); ar(C_1-C_6)alkyl ester which may have at least on suitable substituent(s)

(e.g. benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenethyl ester, trityl ester, benzhydryl ester, bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester, and 4-hydroxy-3,5-di-t-butylbenzyl ester); aryl ester which may have at least on suitable substituent(s) (e.g. phenyl ester, 4-chlorophenyl ester, tolyl ester, t-butylphenyl ester, xylyl ester, mesityl ester, and cumenyl ester); and phthalidyl ester.

More preferable example of the protected carboxy thus defined may be phenyl(C_1-C_4)alkoxycarbonyl which may have a nitro group and (C_2-C_4)alkenyloxycarbonyl, and the most preferable one may be 4-nitrobenzyloxycarbonyl and allyloxycarbonyl.

Suitable "hydroxy(C_1-C_6)alkyl" may include straight or branched C_1-C_6-alkyl having hydroxy group such as hydroxymethyl, hydroxyethyl, hydroxypropyl, 1-(hydroxymethyl)ethyl, 1-hydroxy-1-methylethyl, hydroxybutyl, hydroxypentyl, and hydroxyhexyl, in which more preferable example may be hydroxy(C_1-C_4)-alkyl and the most preferable one may be 1-hydroxyethyl for R^2 and 2-hydroxyethyl for R^4.

Suitable "protected hydroxy(C_1-C_6)alkyl" means aforementioned hydroxy(C_1-C_6)alkyl, in which the hydroxy group is protected by a conventional hydroxy-protective group such as those mentioned in the explanation of imino-protective group as mentioned below; and further ar(C_1-C_4)alkyl such as mono- or di- or triphenyl(C_1-C_6)alkyl (e.g. benzyl, benzhydryl, and trityl; trisubstituted silyl such as tri(C_1-C_6)alkylsilyl (e.g. trimethylsilyl, triethylsilyl, . isopropyldimethylsilyl, t-butyldimethylsilyl, and diisopropylmethylsilyl), triarylsilyl (e.g. triphenylsilyl), and triar(C_1-C_6)alkylsilyl (e.g. tribenzylsilyl).

More preferable example of "protected hydroxy (C_1-C_6)alkyl" thus defined may be carbamoyloxy(C_1-C_4)alkyl, [phenyl (or nitrophenyl)(C_1-C_4)alkoxy]carbonyloxy(C_1-C_4)alkyl, [triphenyl(C_1-C_4)alkoxy](C_1-C_4)alkyl and [tri(C_1-C_4)alkylsilyl]oxy(C_1-C_4)alkyl, and the most preferable one may be 1-(4-nitrobenzyloxycarbonyloxy)ethyl for R^2 and 2-carbamoyloxyethyl for R^4.

Suitable "C_1-C_6- alkyl" may include straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, and hexyl, in which more preferable example may be C_1-C_4 alkyl and the most preferable one may be methyl.

Suitable "C_1-C_6alkyl having suitable substituent(s)" may include protected or unprotected hydroxy (C_1-C_6)alkyl; protected or unprotected hydroxy(C_1-C_6)alkyl having protected or unprotected amino; halo(C_1-C_6)-alkyl; protected or unprotected carbamoyl(C_1-C_6)alkyl; protected or unprotected amino(C_1-C_6)alkyl; protected or unprotected ureido(C_1-C_6)alkyl; protected or unprotected ureidocarbonyl(C_1-C_6)alkyl;and tiazolyl-(C_1-C_6)alkyl.

Suitable protected or unprotected hydroxy(C_1-C_6)alkylhaving protected or unprotected amino means aforementioned hydroxy(C_1-C_6)alkyl having amino group such as 1-amino-1-hydroxymethyl, 2-amino-1-hydroxyethyl, 1-amino-2-hydroxyethyl, 3-amino-2-hydroxypropyl, 2-amino-3-hydroxypropyl, 4-amino-3-hydroxybutyl, 5-amino-4-hydroxypentyl, and 6-amino-5-hydroxyhexyl, in which the amino and/or hydroxy group(s) may be protected by a conventional amino- and/or hydroxy-protective group(s) as mentioned below or above.

More-preferable example of protected or unprotected hydroxy(C_1-C_6)alkyl which has protected or unprotected amino thus defined may be hydroxy(C_1-C_4)alkyl having amino or phenyl(or nitrophenyl)(C_1-C_4)-alkoxycarbonylamino, and the most preferable one may be 3-amino-2-hydroxypropyl and 2-hydroxy-3-(4-nitrobenzyloxycarbonyl)aminopropyl.

Suitable "halo(C_1-C_6)alkyl" may include straight or branched C_1-C_6-alkyl having at least one (preferably one to three) halogen (e.g. chlorine, bromine, iodine, fluorine) such as chloromethyl, fluoromethyl, dichloromethyl, dibromomethyl, diiodomethyl, difluoromethyl, trifluoromethyl, chloroethyl, chlorofluoroethyl, difluoroethyl, trifluoroethyl, chloropropyl, difluoropropyl, trichlorobutyl, chloropentyl, and chlorohexyl, in which more preferable example may be dihalo(C_1-C_4)alkyl and the most preferable one may be difluoromethyl.

Suitable "carbamoyl(C_1-C_6)alkyl" may include straight or branched lower alkyl having carbamoyl group such as carbamoylmethyl, carbamoylethyl, carbamoylpropyl, 1-(carbamoylmethyl)ethyl, 1-carbamoyl-1-methylethyl, carbamoylbutyl, carbamoylpentyl, and carbamoylhexyl, in which more preferable example may be carbamoyl(C_1-C_4)alkyl and the most preferable one may be carbamoylmethyl and 1-carbamoyl-1-methylethyl.

Suitable "protected carbamoyl(C_1-C_6)alkyl" means aforementioned carbamoyl(C_1-C_6)alkyl, in which the carbamoyl group is protected by a conventional carbamoyl-protective group such as mono(or di or tri)halo-(C_1-C_6)alkanoyl (e.g. trichloroacetyl), ar(C_1-C_6-alkyl which may have suitable substituent(s), for example, mono(or di or tri)phenyl(lower)alkyl (e.g. benzyl, phenethyl, benzhydryl, and trityl), mono(or di) C_1-C_6-alkoxyphenyl(C_1-C_6)alkyl (e.g. 2,4-dimethoxybenzyl), bis (C_1-C_6- alkoxyphenyl)(C_1-C_6)alkyl [e.g. bis(4-methoxyphenyl)methyl], and halosulfonyl (e.g. chlorosulfonyl), in which more preferabl one may be trihalo-(C_1-C_4)alkanoyl, bis [(C_1-C_4)alkoxyphenyl](C_1-C_4)alkyl and halosulfonyl.

More preferable example of "protected carbamoyl(C_1-C_6)alkyl" thus defined may be trihalo(C_1-C_4)-alkanoylcarbamoyl(C_1-C_4)alkyl, N-[bis{(C_1-C_4)alkoxyphenyl}(C_1-C_4)alkyl]carbamoyl(C_1-C_4)alkyl and halosulfonylcarbamoyl(C_1-C_4)alkyl.

Suitable "amino(C_1-C_6)alkyl" may include straight or branched C_1-C_6- alkyl having amino group such as aminomethyl, 1-(or 2-)aminoethyl, aminopropyl, aminobutyl, 2-amino-1,1-dimethylethyl, 1-(or 2- or 3-)amino-1-(or 2-)methylpropyl, aminopentyl, and aminohexyl, in which more preferable example may be amino(C_1-C_4)alkyl, and the most preferable one may be 2-aminoethyl and 2-amino-1,1-dimethylethyl.

Suitable "protected amino(C_1-C_6)alkyl" means aforementioned amino(C_1-C_6)alkyl, in which the amino group is protected by a conventional amino-protective group such as those mentioned in the explanation of protected hydroxy(C_1-C_6)alkyl as mentioned above, in which more preferable example may be phenyl(or nitrophenyl)(C_1-C_4)alkoxycarbonyl and C_1-C_4 alkylsulfonyl, and the most preferable one may be 4-nitrobenzyloxycarbonyl and methylsulfonyl.

More preferable example of "protected amino(C_1-C_6)alkyl" thus defined may be N-[phenyl(or nitrophenyl)(C_1-C_4)alkoxycarbonyl]amino(C_1-C_4)alkyl and (C_1-C_4)alkylsulfonylamino(C_1-C_4)alkyl, and the most preferable one may be 2-(4-nitrobenzyloxycarbonylamino)ethyl, 1,1-dimethyl-2-(4-nitrobenzyloxycarbonylamino)ethyl and 2-(methylsulfonylamino)ethyl.

Suitable "ureido(C_1-C_6)alkyl" may include straight or branched C_1-C_6- alkyl having ureido group, such as ureidomethyl, ureidoethyl, ureidopropyl, 1-(ureidomethyl)ethyl, 1-ureido-1-methylethyl, ureidobutyl, 1,1-dimethyl-2-ureidoethyl, ureidopentyl, and ureidohexyl, in which more preferable example may be ureido(C_1-C_4)alkyl and the most preferable one may be 2-ureidoethyl and 1,1-dimethyl-2-ureidoethyl.

Suitable "protected ureido(C_1-C_6)alkyl" means aforementioned ureido(C_1-C_6)alkyl, in which the ureido group is protected by a conventional ureido-protective group such as ar(C_1-C_6)alkyl which may have suitable substituent(s), for example, mono(or di or tri)phenyl(lower)alkyl (e.g. benzyl, phenethyl, benzhydryl, trityl, etc.), mono(or di) C_1-C_6-alkoxyphenyl(C_1-C_6)alkyl (e.g. 2,4-dimethoxybenzyl), and bis(C_1-C_6- alkoxyphenyl)(C_1-C_6)alkyl[e.g. bis(4-methoxyphenyl)methyl], in which more preferable one may be phenyl(C_1-C_4)alkyl.

Suitable "ureidocarbonyl(C_1-C_6)alkyl" may include straight or branched C_1-C_6-alkyl having ureidocarbonyl group, such as ureidocarbonylmethyl, ureidocarbonylethyl, ureidocarbonylpropyl, 1-(ureidocarbonylmethyl)ethyl, 1-ureidocarbonyl-1-methylethyl, ureidocarbonylbutyl, 1,1-dimethyl-2-ureidocarbonylethyl, ureidocarbonylpentyl, and ureidocarbonylhexyl, in which more preferable one may be ureidocarbonylmethyl.

Suitable "protected ureidocarbonyl(C_1-C_6)alkyl" means aforementioned ureidocarbonyl(C_1-C_6)alkyl, in which the ureido group is protected by a conventional ureido-protective group such as ar(C_1-C_6)alkyl which may have suitable substituent(s), for example, mono(or di or tri)phenyl(C_1-C_6)alkyl (e.g. benzyl, phenethyl, benzhydryl, and trityl), mono(or di) C_1-C_6-alkoxyphenyl(C_1-C_6)alkyl (e.g. 2,4-dimethoxybenzyl), bis(C_1-C_6-alkoxyphenyl)(C_1-C_6)alkyl [e.g. bis(4-methoxyphenyl)methyl], in which more preferable one may be phenyl-(C_1-C_4)alkyl.

Suitable "triazolyl(lower)alkyl" may include straight or branched C_1-C_6-alkyl having triazolyl group as mentioned below such as triazolylmethyl, triazolylethyl, triazolylpropyl, 1-(triazolylmethyl)ethyl, 1-triazolyl-1-methylethyl, triazolylbutyl, triazolylpentyl, and triazolylhexyl, in which more preferable example may be triazolyl(C_1-C_4)alkyl and the most preferable one may be 1,2,4-triazolylmethyl.

Suitable "heterocyclic group" means saturated or unsaturated, 5 or 6-membered hetero monocyclic group containing 1 to 4, nitrogen atom(s) or containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s).

Preferable heterocyclic group may be

unsaturated, 5 or 6-membered, heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, imidazolinyl, pyrazolyl, pyrazolinyl, pyridyl, pyridyl N-oxide, pyridinio, dihydropyridyl, tetrahydropyridyl [e.g. 1,2,3,6-tetrahydropyridyl], pyrimidinyl, pyrimidinio, pyrazinyl, pyrazinio, pyridazinyl, pyridazinio, triazinyl [e.g. 1,3,5-triazinyl, 1,2,4-triazinyl and 1,2,3-triazinyl], tetrahydrotriazinyl [e.g. 1,2,5,6-tetrahydro-1,2,4-triazinyl, and 1,4,5,6-tetrahydro-1,2,4-triazinyl, triazinio, triazolyl [e.g. 1H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, and 2H-1,2,3-triazolyl], triazolio, tetrazinyl, tetrazinio,tetrazolyl [e.g. 1H-tetrazolyl and 2H-tetrazolyl], and tetrazolio;

saturated, 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolidinyl, imidazolidinyl, piperidino, and piperazinyl;

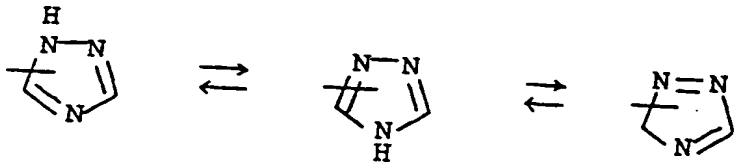
unsaturated, 5 or 6-membered, heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, thiazolio, isothiazolyl, thiadiazolyl [e.g. 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl], thiadiazolio, thiazolinyl, and dihydrothiazinyl;

wherein said heterocyclic group may be substituted by suitable substituent(s) such as C_1-C_6- alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl,and hexyl); amino or amino(C_1-C_6)alkyl [e.g.

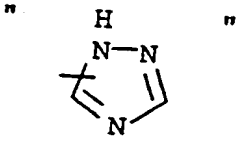
aminomethyl, 1-(or 2-)aminoethyl, aminopropyl, aminobutyl, 1-(or 2- or 3-)amino-1-(or 2-)methylpropyl, aminopentyl, and aminohexyl,], in which said amino moiety may be substituted by one or two C_1-C_6 alkyl group(s) as mentioned above; and further, in case that said heterocyclic group is pyrrolidinyl, the imino-moiety of pyrrolidine ring may be protected by a conventional imino-protective group as mentioned below.

More preferable "heterocyclic group optionally substituted by suitable substituent(s)" thus defined means saturated or unsaturated 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom-(s), or containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), which may have C_1-C_4 alkyl, N,N-di(C_1-C_4)alkylamino(C_1-C_4)alkyl or phenyl(or nitrophenyl)(C_1-C_4)alkoxycarbonyl, and the most preferable one may be pyridyl, tetrazolyl, pyrrolidinyl, 1-(4-nitrobenzyloxycarbonyl)pyrrolidinyl, thiadiazolyl, 1-methyl-1H-tetrazolyl and 1-{2-(N,N-dimethylamino)ethyl}-1H-tetrazolyl.

Furthermore, when the heterocyclic group as stated above is, for example, 1,2,4-triazolyl group, there are tautomeric isomers as shown by the following equilibrium :



All of the above tautomeric isomers are included within the scope of the present invention and in the present specification, however, the object and intermediate compounds including the group of such tautomeric isomers are represented by using one of the expressions therefor, i.e. 2H-(or 1H-)1,2,4-triazolyl and the formula :



only for the convenient sake.

Suitable "C_1-C_6-alkanimidoyl" may be straight or branched one such as formimidoyl, acetimidoyl, propionimidoyl, butyrimidoyl, isovalerimidoyl, pentanimidoyl, and hexanimidoyl, in which more preferable one may be (C_1-C_4)alkanimidoyl and the most preferable one may be acetimidoyl.

Suitable "C_1-C_6-alkylsulfonyl" may include methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl, pentylsulfonyl, and hexylsulfonyl, in which more preferablo example may be (C_1-C_4)alkylsulfonyl and the most preferable one may be methylsulfonyl.

Suitable imino-protective group in "protected imino" may be the same as those for the "imino-protective group" as mentioned below.

Suitable "imino-protective group" may include acyl such as carbamoyl, aliphatic acyl, aromatic acyl, heterocyclic acyl and aliphatic acyl substituted with aromatic or heterocyclic group(s) derived from carboxylic, carbonic, sulfonic and carbamic acids.

The aliphatic acyl may include saturated or unsaturated, acyclic or cyclic ones, for example, alkanoyl such as C_1-C_6-alkanoyl (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, and hexanoyl), alkylsulfonyl such as C_1-C_6-alkylsulfonyl (e.g. mesyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, isobutylsulfonyl, pentylsulfonyl, and hexylsulfonyl), carbamoyl, N-alkylcarbamoyl (e.g. methylcarbamoyl, and ethylcarbamoyl), alkoxycarbonyl such as C_1-C_6-alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, and t-butoxycarbonyl), alkenyloxycarbonyl such as C_1-C_6-alkenyloxycarbonyl (e.g. vinyloxycarbonyl, and allyloxycarbonyl), alkenoyl such as C_1-C_6-alkenoyl (e.g. acryloyl, methacryloyl, and crotonoyl), cycloalkanecarbonyl such as cyclo(C_1-C_6)alkanecarbonyl (e.g. cyclopropanecarbonyl, cyclopentanecarbonyl, and cyclohexanecarbonyl).

The aromatic-acyl may include aroyl (e.g. benzoyl, toluoyl, and xyloyl), N-arylcarbamoyl (e.g. N-phenylcarbamoyl, N-tolylcarbamoyl, and N-naphthylcarbamoyl), arenesulfonyl (e.g. benzenesulfonyl, and tosyl).

The heterocyclic acyl may include heterocycliccarbonyl (.g. furoyl, thenoyl, nicotinoyl, isonicotinoyl, thiazolylcarbonyl, thiadiazolylcarbonyl, and tetrazolylcarbonyl).

The aliphatic acyl substituted with aromatic group(s) may includ aralkanoyl such as phenyl(lower)-alkanoyl (e.g. phenylacetyl, phenylpropionyl, and phenylhexanoyl), aralkoxycarbonyl such as phepyl(lower)-alkoxycarbonyl (e.g. benzyloxycarbonyl, and phenethyloxycarbonyl), aryloxyalkanoyl such as phenoxy (C_1-C_6)alkanoyl (e.g. phenoxyacetyl, and phenoxypropionyl).

The aliphatic acyl substituted with heterocyclic group(s) may include heterocyclic-alkanoyl such as heterocyclic-(C_1-C_6)alkanoyl (e.g. thienylacetyl, imidazolylacetyl, furylacetyl, tetrazolylacetyl, thiazolylacetyl, thiadiazolylacetyl, thienylpropionyl, and thiadiazolylpropionyl.

These acyl groups may be further substituted with one or more suitable substituents such as C_1-C_6-alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, pentyl, and hexyl), halogen (e.g. chlorine, bromine, iodine, fluorine), C_1-C_6-alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentyloxy, and hexyloxy), C_1-C_6-alkylthio (e.g. methylthio, ethylthio, propylthio, isopropylthio, butylthio, pentylthio, and hexylthio), and nitro, and preferable acyl having such substituent(s) may be mono(or di or tri)haloalkanoyl (e.g. chloroacetyl, bromoacetyl, dichloroacetyl, and trifluoroacetyl), mono(or di or tri)haloalkoxycarbonyl (e.g. chloromethoxycarbonyl, dichloromethoxycarbonyl, and 2,2,2-trichloroethoxycarbonyl), nitro-(or halo or C_1-C_6-alkoxy)-aralkoxycarbonyl (e.g. nitrobenzyloxycarbonyl, chlorobenzyloxycarbonyl, and methoxybenzyloxycarbonyl), mono (or di or tri)-halo(C_1-C_6)alkylsulfonyl (e.g. fluoromethylsulfonyl, difluoromethylsulfonyl, trifluoromethylsulfonyl, and trichloromethylsulfonyl).

More preferable example of "imino-protective group" thus defined may be (C_2-C_4)alkenyloxycarbonyl and phenyl(C_1-C_4)alkoxycarbonyl which may have a nitro group, and the most preferable one may be allyloxycarbonyl and 4-nitrobenzyloxycarbonyl.

Suitable "C_1-C_4-alkylene" may include straight or branched one such as methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, methylmethylene, ethylethylene, and propylene, in which more preferable example may be C_1-C_4 alkylene and the most preferable one may be methylene.

Suitable "mercapto-protective group" may include acyl as mentioned above, ar(C_1-C_6)alkyl such as mono-or di- or triphenyl(C_1-C_6)alkyl (e.g. benzyl, phenethyl, benzhydryl, and trityl), in which more preferable example may be C_1-C_4 alkanoyl, aroyl and triphenyl(C_1-C_4)alkyl, and the most preferable one may be benzoyl.

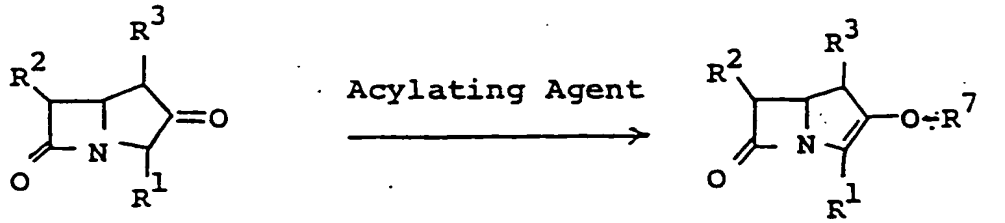
The processes for the preparation of the object derivatives (I) of the present invention are explained in detail in the following.

(1) Process 1 :

The derivatives (I) or salts thereof can be prepared by reacting the compound (II) or a reactive derivative at the oxo group thereof or salts thereof with the compound (III) or salts thereof.

Suitable salts of the compound (II) may be salts with bases such as those given for the derivatives (I).

The reactive derivative at the oxo group of the compound (II) can be represented by the following formula (II'), which is preferably used in this reaction and can be prepared by reacting the compound (II) or salts thereof with an acylating agent.



(II) or salts thereof

(II') or salts thereof

in which

R^1, R^2 and R^3 are each as defined above, and

R^7 is acyl as exemplified for the imino-protective group and further O,O-substituted

phosphono derived from, for example, organic phosphoric acid mentioned hereinbelow.

Suitable acylating agents may include conventional ones which can introduce the acyl group as mentioned above into the compound (II), and preferable acylating agents may be organic sulfonic or phosphoric acid or its reactive derivative such as acid halide, and acid anhydride, for example, arenesulfonyl halide (e.g. benzenesulfonyl chloride, p-toluenesulfonyl chloride, p-nitrobenzenesulfonyl chloride, and p-bromobenzenesulfonyl chloride), arenesulfonic anhydride (e.g. benzenesulfonic anhydride, p-toluenesulfonic anhydride, and p-nitrobenzenesulfonic anhydride), C_1-C_6-alkanesulfonyl halide which may have additional halogen (e.g. methanesulfonyl chloride, ethanesulfonyl chloride, and trifluoromethanesulfonyl chloride), C_1-C_6-alkanesulfonic anhydride which may have halogen (e.g.,methanesulfonic anhydride, ethanesulfonic anhydride, and trifluoromethanesulfonic anhydride), di(C_1-C_6)alkyl phosphorohaloridate (e.g. diethyl phosphorochloridate), diaryl phosphorohaloridate (e.g. diphenyl phosphorochloridate).

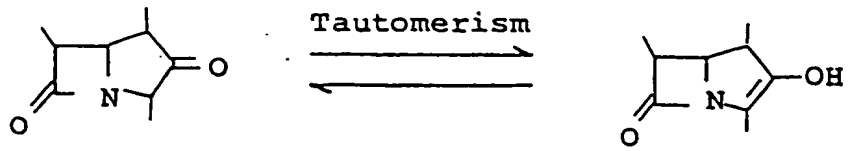
This acylation reaction is usually carried out in a conventional solvent-which does not adversely influence the reaction such as acetone, dioxane, acetonitrile, chloroform, dichloromethane, hexamethylphosphoramide, dichloroethane, tetrahydrofuran, ethyl acetate, dimethylsulfoxide, N,N-dimethylformamide, and pyridine, or a mixture thereof.

When the acylating agent is used in a free acid form or its salt form in this reaction, the reaction is preferably carried out in the presence of a conventional condensing agent such as carbodiimide compounds (e.g. N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide, N,N'-dicyclohexylcarbodiimide, N-cyclohexyl-N'-morpholinoethylcarbodiimide, N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide, and N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide); N,N'-carbonyldiimidazole, N,N'-carbonylbis(2-methylimidazole); keteneimine compounds (e.g. pentamethyleneketene-N-cyclohexylimine, diphenylketene-N-cyclohexylimine); ethoxyacetylene; 1-alkoxy-1-chloroethylene; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride; phosphorus trichloride; thionyl chloride; oxalyl chloride; a combination of triphenylphosphine with carbon tetrachloride or diazenedicarboxylate; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, and phosphorus oxychloride.

This acylation reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal bicarbonate (e.g. sodium bicarbonate, and potassium bicarbonate), alkali metal carbonate (e.g. sodium carbonate, and potassium carbonate), alkaline earth metal carbonate (e.g. magnesium carbonate, and calcium carbonate), tri(lower)alkylamine (e.g. trimethylamine, triethylamine, and N,N-diisopropyl-N-ethylamine), pyridine compounds [e.g. pyridine, picoline, lutidine, and N,N-di(C_1-C_6)alkylaminopyridine such as N,N-dimethylaminopyridine], quinoline, N- C_1-C_6-alkylmorphorine (e.g. N-methylmorphorine), N,N-di(C_1-C_6)alkylbenzylamine (e.g. N,N-dimethylbenzylamine).

The reaction temperature of this acylation reaction is not critical and the reaction is usually carried out under from cooling to warming.

With regard to the compound (II), it is to be noted that the 3,7-dioxo-1-azabicyclo[3.2.0]heptane ring system of the following formula (IIA) is well known to lie in tautomeric relation with the 3-hydroxy-7-oxo-1-azabicyclo[3.2.0]hept-2-ene ring system of the following formula (IIB), and accordingly, it is to be understood that both of these ring systems are substantially the same.



(IIA) (IIB)

The compound (II') or salts thereof can be used with or without isolation for the subsequent reaction with the compound (III) or salts thereof.

Suitabl salts of the compound (III) may be the same as thos for the derivatives (I) and silver salt.

The reaction of the compound (II) or its reactive derivative or salts thereof with the compound (III) or salts thereof can be carried out in the presence of an organic or inorganic base such as thos given in the explanation of the acylation reaction as stated above.

This reaction can be carried out in a conventional solvent which does not adversely influence the reaction such as those given in the explanation of the acylation reaction.

The reaction temperature is not critical and the reaction is usually carried out under from cooling to warming.

(2) Process 2 :

The derivative (I-b) or salts thereof can be prepared by subjecting the derivative (I-a) or salts thereof to elimination reaction of the carboxy-protective group on R_a^1 .

Suitable salts of the derivative (I-b) may be the same as those for the derivatives (I), and those of the derivative (I-a) may be salts with bases such as those given for the derivatives (I).

The present reaction is usually carried out by a conventional method such as hydrolysis, and reduction.

(i) Hydrolysis :

Hydrolysis is preferably carried out in the presence of a base or an acid. Suitable base may include an alkali metal hydroxide (e.g. sodium hydroxide, and potassium hydroxide),), an alkaline earth metal hydroxide (e.g. magnesium hydroxide, and calcium hydroxide), alkali metal hydride (e.g. sodium hydride, and potassium hydride), alkaline earth metal hydride (e.g. calcium hydride,), alkali metal alkoxide (e.g. sodium methoxide, sodium ethoxide, and potassium t-butoxide), an alkali metal carbonate (e.g. sodium carbonate, and potassium carbonate), an alkaline earth metal carbonate (e.g. magnesium carbonate, and calcium carbonate,), an alkali metal bicarbonate (e.g. sodium bicarbonate, and potassium bicarbonate).

Suitable acid may include an organic acid (e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, benzenesulfonic acid, and p-toluenesulfonic acid) and an inorganic acid (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, and phosphoric acid). The acidic hydrolysis using trifluoroacetic acid is usually accelerated by addition of cation trapping agent (e.g. phenol, and anisole). In case that the hydroxy-protective group is tri(C_1-C_6)alkylsilyl, the hydrolysis can be carried out in the presence of tri(lower)-alkylammonium fluoride (e.g. tributylammonium fluoride).

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, dichloromethane, alcohol (e.g. methanol, and ethanol), tetrahydrofuran, dioxane, acetone, or a mixture thereof. A liquid base or acid can be also used as the solvent.

The reaction temperature is not critical and the reaction is usually carried out under from cooling to heating.

(ii) Reduction :

The reduction method applicable for this elimination reaction may include, for example, reduction by using a combination of a metal (e.g. zinc, and zinc amalgam) or a salt of chrome compound (e.g. chromous chloride, and chromous acetate) and an organic or inorganic acid (e.g. acetic acid, propionic acid, hydrochloric acid, and sulfuric acid); and conventional catalytic reduction in the presence of a conventional metallic catalyst such as palladium catalysts (e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, palladium hydroxide on carbon, colloidal palladium, palladium on barium sulfate, and palladium on barium carbonate), nickel catalysts (e.g. reduced nickel, nickel oxide, and Raney nickel), platinum catalysts (e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, and platinum wire).

In case that the catalytic reduction is applied, the reaction is preferably carried out around neutral condition.

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, alcohol (e.g. methanol, ethanol, and propanol), dioxane, tetrahydrofuran, acetic acid, buffer solution (e.g. phosphate buffer, and acetate buffer) or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under from cooling to warming.

In case that the carboxy-protective group is allyl group, it can be deprotected by hydrogenolysis using a palladium compound.

Suitable palladium compound used in this reaction may be palladium on carbon, palladium hydroxide on carbon, palladium chloride, a palladium-ligand complex such as tetrakis(triphenylphosphine)palladium(0), bis(dibenzylideneacetone)palladium(0), di[1,2-bis(diphenyl phosphino)ethane]palladium(0), tetrakis(triphenyl phosphite)palladium(0), and tetrakis(triethyl phosphite)palladium(0).

This reaction can preferably be carried out in the presence of a scavenger of allyl group generated in situ, such as amine (e.g. morpholin , and N-methylaniline), an activated methylene compound (e.g. dimedone, benzoylacetate, and 2-methyl-3-oxovaleric acid), a cyanohydrin compound (e.g. α-tetrahydropyranyloxybenzyl cyanide), C_1-C_6-alkanoic acid or a salt thereof (e.g. formic acid, acetic acid, ammonium formate, and sodium acetate), and N-hydroxysuccinimide.

This reaction can be carried out in the presence of a base such as C_1-C_6-alkylamine (e.g. butylamine, and triethylamine), and pyridine.

When palladium-ligand complex is used in this reaction, the reaction can preferably be carried out in the presence of the corresponding ligand (e.g. triphenylphosphine, triphenyl phosphite, and triethyl phosphite).

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, dioxane, tetrahydrofuran, acetonitrile, chloroform, dichloromethane, dichloroethane, and ethyl acetate, or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under from cooling to warming.

The elimination reaction can be selected according to the kind of carboxy-protective group to be eliminated.

The present process includes within the scope thereof a case that the hydroxy- and/or amino- and/or imino-protective group(s) for R^2, R^4, R^5 and X are removed at the same time during the reaction.

(3) Process 3:

The derivative (I-d) or salts thereof can be prepared by subjecting the derivative (I-c) or salts thereof to elimination reaction of the imino-protective group of R_a^5 .

Suitable salts of the derivative (I-c) may be salts with bases such as those given for the derivatives (I), and those of the derivative (I-d) may be the same salts with bases and acids for the derivatives (I).

This reaction is usually carried out by a conventional method such as hydrolysis, and reduction.

The method of hydrolysis and reduction, and the reaction conditions (e.g. reaction temperature, and solvent,) are substantially the same as those illustrated for elimination reaction of the carboxy-protective group of the derivative (I-a) in Process 2, and therefore are to be referred to said explanation.

The present process includes within the scope thereof a case that the carboxy- and/or hydroxy- and/or amino- and/or imino-protective group(s) for R^1, R^2, R^4 and X are removed at the same time during the reaction.

(4) Process 4:

The derivative (I-f) or salts thereof can be prepared by subjecting the derivative (I-e) or salts thereof to elimination reaction of the hydroxy-protective group on R_a^2 .

Suitable salts of the derivatives (I-e) and (I-f) may be the same as those for the derivatives (I).

This reaction is usually, carried out by a conventional method such as hydrolysis, and reduction.

The method of hydrolysis and reduction, and the reaction conditions (e.g. reaction temperature, and solvent,) are substantially the same as those illustrated for elimination reaction of the carboxy-protective group of the derivative (I-a) in process 2, and therefore are to be referred to said explanation.

The present process includes within the scope thereof a case that the carboxy- and/or amino- and/or imino-protective group(s) for R^1, R^4, R^5 and X are removed at the same time during the reaction.

(5) Process 5:

The derivative (I-g) or salts thereof can be prepared by reacting the derivaive (I-d) or salts thereof with lower alkanimidoylating agent.

Suitable salts of the derivative (I-g) may be the same salts with bases for the derivatives (I).

Suitable C_1-C_6-alkanimidoylating agent may be conventional ones which can introduce the C_1-C_6-alkanimidoyl group as mentioned above into the derivative (I-d), and said preferable agent may be C_1-C_6-alkyl(lower)alkanimidate (e.g. methyl formimidate, ethyl formimidate, methyl acetimidate, ethyl acetimidate, ethyl propionimidate, ethyl butyrimidate, ethyl isovalerimidate, ethyl pentanimidate, and ethyl hexanimidate), (C_1-C_6)alkanimidoyl halide (e.g. formimidoyl chloride, formimidoyl bromide, acetimidoyl chloride, acetimidoyl bromid , propionimidoyl chloride, butyrimidoyl chloride, isovalerimidoyl chloride, pentanimidoyl chloride, and hexanimidoyl chloride), or an acid addition salt thereof.

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as tetrahydrofuran, dioxane, water, methanol, ethanol, buffer solution (e.g. phosphate buffer), or a mixture thereof.

The reaction temperature is not critical, and the reaction is usually carried out under from cooling to warming.

Methods A and B for preparing the new starting compound (III) or salts thereof are explained in detail in the following.

(A) Method A

The compound (III-a) or salts thereof can be prepared by reacting the compound (IV) or a reactive derivative at the hydroxy group thereof or salts thereof with the compound (V) or salts thereof.

Suitable Salts of the compounds (III-a), (IV) and (V) may be the same as those for the compound (III).

Suitable reactive derivative at the hydroxy group of the compound (IV) may include a conventional one such as halide (e.g. chloride, bromide, and iodide,), sulfonate (e.g. methanesulfonate, benzenesulfonate, and toluenesulfonate), in which more preferable example may be sulfonate.

The starting compound (IV) or a reactive derivative at the hydroxy group thereof of this method is new and can be prepared by the methods described in the Preparations mentioned below, or by a conventional process.

Preferable example of the compound (V) may be ar(C_1-C_6)alkanethiol such as mono- or di- or triphenyl-(C_1-C_6)alkanethiol (e.g. phenylmethanethiol, diphenylmethanethiol, and triphenylmethanethiol), thio(C_1-C_6)-alkanoic S-acid (e.g. thioacetic S-acid), thioarenoic S-acid (e.g. thiobenzoic S-acid), in which more preferable example may be triphenyl(C_1-C_4)alkanethiol, thio(C_1-C_4)alkanoic S-acid and thio(C_6-C_{10})arenoic S-acid, and the most preferable one may be thiobenzoic S-acid.

In case that the compound (V) may be ar(C_1-C_6)alkanethiol, the starting compound (IV) of the present reaction is preferably used in a form of its reactive derivative at the hydroxy group, and in such a case, this reaction is usually carried out in the presence of an organic or inorganic base such as those exemplified in the explanation of Process 1.

In case that suitable example of compound (V) may be thio(C_1-C_6)alkanoic S-acid or thioarenoic S-acid, this reaction is preferably carried out in the presence of a conventional condensing agent such as combination of triarylphosphine (e.g. triphenylphosphine) and di(lower)alkyl azodicarboxylate (e.g. diethyl azodicarboxylate).

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as dichloromethane, methanol, ethanol, propanol, pyridine, N,N-dimethylformamide, and tetrahydrofuran or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under from cooling to warming.

In this method, the configuration on the carbon atom substituted with the hydroxy group of the compound (IV) is inverted in the compound (III-a).

(B) Method B

The compound (III) or salts thereof can be prepared by subjecting the compound (III-a) or salts thereof to elimination reaction of the mercapto-protective group.

This elimination reaction can be carried out by a conventional method as described below, which can be selected according to the kind of mercapto-protective group to be eliminated.

In case that the protective groups may be ar(lower)alkyl group, it can generally be eliminated by treating, for example, with a silver compound (e.g. silver nitrate, and silver carbonate).

The reaction with the silver compound as stated above is preferably carried out in the presence of an organic base (e.g. pyridine).

The resultant silver salt of compound (III) can be transformed into its alkali metal salt, if necessary, by reacting with alkali metal halide (e.g. sodium iodide, and potassium iodide)

Further, in case that the protective groups may be acyl group, it can generally be eliminated by solvolysis such as hydrolysis using an acid or base, alcoholysis using a base.

Suitable acid or base used in these reactions may be the same such as those given in the explanation of hydrolysis of the Process 2.

The hydrolysis is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, alcohol (e.g. methanol, and ethanol), pyridine, and N,N-dimethylformamide, or a

mixture thereof, and further in case that the base or acid to be used is in liquid, it can also be used as a solvent.

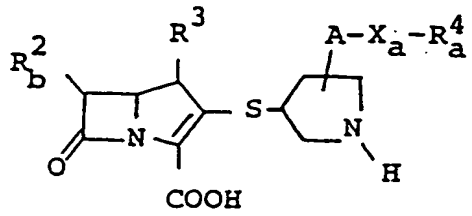
The alcoholysis is usually carried put in a conventional alcohol such as methanol, and ethanol.

The reaction temperature is not critical and the reaction is usually carried out under from cooling to warming.

The object derivatives (I), and the compounds (III) and (III-a) obtained according to the Processes 1 to 5, and Methods A and B as explained above can be isolated and purified in a conventional manner, for example, extraction, precipitation, fractional crystallization, recrystallization, and chromatography.

The object derivatives (I) and the pharmaceutically acceptable salts thereof of the present invention are novel and exhibit high antimicrobial activity, inhibiting the growth of a wide variety of pathogenic microorganisms, and further , are very stable against dehydropeptidase and show high urinary excretion, therefore have high potential for the treatment of various infectious diseases.

In the present invention, the object derivatives (I) possessing more potent antimicrobial activity can be represented by the following formula :



(I')

in which R_b^2 , R^3 and A are each as defined above,

R_a^4 is C_1-C_6-alkyl having suitable substituent(s), heterocyclic group optionally substituted by suitable substituent(s), or lower alkylsulfonyl, and

X_a is sulfur, oxygen or imino,

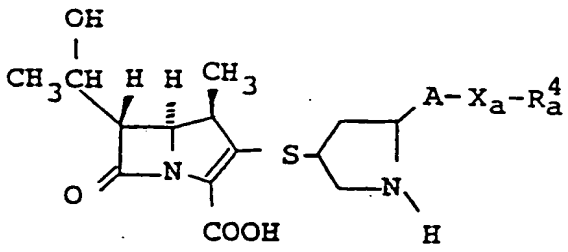
provided that

when X is oxygen,

then R^4 is not "protected or unprotected ureido(lower)alkyl",

and pharmaceutically acceptable salts thereof.

Particularly, the compounds (I) possessing the most potent antimicrobial activity can be represented by the following formula :



in which R_a^4 , A and X_a are each as defined above, and pharmaceutically acceptable salts thereof.

Now, in order to show the utility of the object derivatives (I), the test data on antimicrobial activity of the representative compound of the object derivatives (I) of this invention is shown in the following.

in vitro Antimicrobial Activity

Test Method :

in vitro Antimicrobial Activity was determined by the two-fold agar-plat dilution method as described below.

One loopful of an overnight culture of a test strain in Trypticase-soy broth (10^6 viable cells per ml) was streaked on heart infusion agar (HI-agar) containing graded concentrations of the test compound, and the minimal inhibitory concentration (MIC) was expressed in terms of μg/mℓ after-incubation at 37 • C for 20 hours.

Test Compound (1) :

(4R,5S,6S)-3-[(2S,4S)-2-(Difluoromethyl)thiomethylpyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid.

Test Result (1)	
Test Strain	MIC (μg/mℓ)
Staphylococcus aureus 3004	0.39

Test Compound (2) :

(4R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-3-[(2S,4S)-2-(2-hydroxyethyloxymethyl)pyrrolidin-4-yl]thio-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid.

Test Result (2)	
Test Strain	MIC (μg/mℓ)
Pseudomonas aeruginosa 26	0.39

For therapeutic administration, the object compounds (I) and the pharmaceutically acceptable salts thereof of the present invention are used in the form of conventional pharmaceutical preparation which contains said compound , as an active ingredient, in admixture with pharmaceutically acceptable carriers such as an organic or inorganic solid or liquid excipient which is suitable for oral, parenteral and external administration. The pharmaceutical preparations may be in solid form such as tablet, granule, powder, capsule, or liquid form such as solution, suspension, syrup, emulsion, and lemonade.

If needed, there may be included in the above preparations auxiliary substances, stabilizing agents, wetting agents and other commonly used additives such as lactose, stearic acid, magnesium stearate, terra alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter, ethylene glycol, tartaric acid, citric acid, and fumaric acid.

While the dosage of the compounds (I) may vary from and also depend upon the age, conditions of the patient, a kind of diseases, a kind of the compounds (I) to be applied. In general, amount between 1 mg and about 4,000 mg or even more per day may be administered to a patient. An average single dose of about 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg, 1000 mg, 2000 mg, of the object compounds (I) of the present invention may be used in treating diseases infected by pathogenic microorganisms.

The following Preparations and Examples are given for the purpose of illustrating this invention in more detail.

Preparation 1

To a solution of (2S,4R)-4-t-butyldimethylsilyloxy-2-methanesulfonyloxymethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (5.21 g) in N,N-dimethylformamide (52 ml) was added potassium thioacetate (1.83 g) and the mixture was stirred at 50-60 • C for 1 hour. The reaction mixture was poured into ice-water (150 ml) and extracted 3 times with ethyl acetate (50 ml). The extracts were combined, washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give a residu . Th residue was subjected to a column chromatography on silica gel (150 g) and eluted with a mixture of n-hexane and ethyl acetate (3:1, V/V). The fractions containing th desired compound were collected and evaporated in vacuo to give (2S,4R)-2-acetylthiomethyl-4-t-butyldimethylsilyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (4.70 g).

IR (Neat) : 1710-1700, 1610, 1530, 1405, 1350,1260, cm^{-1}

NMR ($CDCl_3$, δ) : 0.06 (6H, s), 1.84 (9H, s), 2.35 (3H, s), 5.26 (2H, s), 7.54 (2H, d, J = 8Hz), 8.22 (2H, d, J = 8Hz)

Preparation 2-1)

To a solution of (2S,4R)-2-acetylthiomethyl-4-t-butyldimethylsilyloxy-1-(4-nitrobenzyloxycarbonyl)-pyrrolidine (2 g) in methanol (20 ml) was added 28% sodium methoxide-methanol solution (0.98 ml) with stirring at 2 - 5 °C for 10 minutes. Chlorodifluoromethane was bubbled into the reaction mixture at 40 °C for 4 hours and under refluxing for 2 hours. After neutralizing the solution with glacial acetic acid (0.6 ml), the solution was concentrated under reduced pressure. To the residue were added ethyl acetate (60 ml) and saturated aqueous sodium hydrogen carbonate (30 ml). The separated organic layer was washed in turn with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The resulting residue was subjected to a column chromatography on silica gel (100g) and eluted with a mixture of n-hexane and ethyl acetate (5:1, V/V). The fractions containing the desired compound were collected and evaporated in vacuo to give (2S,4R)-4-t-butyldimethylsilyloxy-2-(difluoromethyl)thiomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.38 g).

IR (Neat) : 1710-1690, 1610, 1530, 1400 cm^{-1}

NMR ($CDCl_3$, δ) : 0.05 (6H, s) 0.86 (9H, s), 1.80-2.15 (2H, m), 5.25 (2H, s), 7.25 (1H, t, J = 28Hz), 7.51 (2H, d, J = 8Hz), 8.21 (2H, d, J = 8Hz)

Preparation 2-2)

To a solution of (2S,4R)-2-acetylthiomethyl-4-t-butyldimethylsilyoxy-1-(4-nitrobenzyloxycarbonyl)-pyrrolidine (2.0 g) in methanol (20 ml) was added 28% sodium methoxide-methanol solution (0.98 ml) under an atmosphere of nitrogen at 0 °C. After stirring at the same temperature for 10 minutes, to this reaction mixture was added 2-iodoacetamide (1.02 g) under the same condition. The mixture was stirred at ambient temperature for 3 hours. The reaction mixture was concentrated under reduced pressure. The resulting residue was dissolved in ethyl acetate (100 ml). The solution was washed with saturated aqueous sodium hydrogen carbonate and saturated sodium chloride successively, dried over anhydrous magnesium sulfate, and evaporated in vacuo to give (2S,4R)-4-t-butyldimethylsilyloxy-2-(carbamoylmethyl)thiomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (2.11 g).

IR (Neat) : 1705 (sh), 1690-1675, 1610, 1525, 1350, 1260 cm^{-1}

NMR ($CDCl_3$, δ) : 0.06 (6H, s), 0.86 (9H, s), 1.88-2.22 (2H, m), 3.22 (2H, s), 5.25 (2H, s), 7.53 (2H, d, J = 8Hz), 8.25 (2H, d, J = 8Hz)

Preparation 3-1)

To a solution of (2S,4R)-4-t-butyldimethylsilyloxy-2-(difluoromethyl)thiomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.36 g) in methanol (30 ml) was added conc. hydrochloric acid (0.47 ml) at ambient temperature and the mixture was stirred at the same temperature for 1 hour. The reaction mixture was concentrated under reduced pressure. The resulting residue was dissolved in ethyl acetate (50 ml). The solution was washed in turn with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure to give (2S,4R)-2-(difluoromethyl)thiomethyl-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.03 g).

IR (Neat) : 3450-3400, 1710-1690, 1610, 1525, 1410 cm^{-1}

NMR ($CDCl_3$, δ) : 1.52-1.95 (2H, m), 2.75-3.50 (2H, m), 4.05-4.70 (2H, m), 5.23 (2H, s), 6.80 (1H, t, J = 56Hz), 7.53 (2H, d, J = 8Hz), 8.22 (2H, d, J = 8Hz)

EI Mass : 278 (M^+-84) , 265 (M^+-97)

Preparation 3-2)

To a solution of (2S,4R)-4-t-butyldimethylsilyloxy-2-(carbamoylmethyl)thiomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (2.10 g) in methanol (40 ml) was added conc. hydrochloric acid (0.72 ml) at ambient temperature. After stirring at the same temperature for 1 hour, this reaction mixture was concentrated under reduced pressure to give a residue. The residue was dissolved in ethyl ac tate (60 ml). The solution was washed with saturated aqueous sodium hydrogen carbonate and saturated aqu ous sodium chloride successively, dried over anhydrous magnesium sulfate, and evaporated in vacuo to give a residue. The residue was washed with a mixture of ethyl acetate (30 ml) and diisopropyl ether (15 ml). The resulting

precipitates w re collected by filtration and air-dried to give (2S,4R)-2-(carbamoylmethyl)thiomethyl-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.08 g).

mp : 118-119 °C

IR (Neat) : 1710, 1610, 1525, 1405, 1350, 1350, 1210 cm^{-1}

NMR (DMSO-d_6, δ) : 1.80-2.15 (2H, m), 2.65-3.05 (2H, m), 3.09 (2H, s), 3.30-3.55 (2H, m), 3.85-4.50 (2H, m), 4.96 (1H, d, J = 4Hz) , 5.24 (2H, s), 7.66 (2H, d, J = 8Hz), 8.26 (2H, d, J = 8Hz)

Mass : 369 (M^+) , 278 (M^+-91)

Preparation 4

To a solution of (2S,4R)-2-(difluoromethyl)thiomethyl-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.01 g) and triphenylphosphine (1.1 g) in tetrahydrofuran (20 ml) was added dropwise a solution of diethyl azodicarboxylate (0.66 ml) in tetrahydrofuran (3 ml) at -10 °C to -5 °C with stirring. The mixture was stirred at the same temperature for 30 minutes. To the solution was added thiobenzoic S-acid (0.49 ml) at the same temperature and the mixture was stirred under ice-cooling for 2 hours. The reaction mixture was concentrated under reduced pressure. The resulting residue was dissolved in ethyl acetate (60 ml). The solution was washed with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride successively, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The resulting residue was chromatographed on silica gel (100 g) eluting with a mixture of n-hexane and ethyl acetate (3:1,V/V). The fractions containing the desired compound were collected and evaporated in vacuo to give (2S,4S)-4-benzoylthio-2-(difluoromethyl)thiomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.01 g).

IR (Neat) : 1710, 1665, 1610, 1525, 1405, 1350, 1210 cm^{-1}

NMR ($CDCl_3$, δ) : 1.45-1.75 (2H, m), 3.20-3.75 (3H, m), 3.85-4.45 (5H, m), 5.25 (2H, s), 6.68 (1H, t, J = 56Hz), 7.40-7.65 (4H, m), 7.80-8.05 (2H, m), 8.23 (2H, d, J = 8Hz)

Preparation 5

To a solution of (2S,4R)-2-(carbamoylmethyl)thiomethyl-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)-pyrrolidine (1.06 g) and triethylamine (0.92 ml) in a mixture of tetrahydrofuran (40 ml) and N,N-dimethylformamide (5 ml) was added dropwise methanesulfonyl chloride (0.44 ml) under ice-cooling. The mixture was stirred at 2 °C for 1 hour and then allowed to stand at ambient temperature for 1 hour. To the reaction mixture was added ethyl acetate (50 ml). The solution was washed with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride successively, dried over anhydrous magnesium sulfate, and evaporated in vacuo to give (2S,4R)-2-(carbamoylmethyl)thiomethyl-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.70 g).

IR (Neat) : 1710-1660, 1610, 1525, 1350, 1175 cm^{-1}

NMR ($CDCl_3$, δ) : 2.05-2.60 (3H, m), 3.03 (3H, s), 5.25 (2H, s), 7.53 (2H, d, J = 8Hz), 8.25 (2H, d, J-8Hz)

Preparation 6

To a suspension of sodium hydride (62.8% in oil) (0.22 g) in N,N-dimethylformamide (5 ml) was added dropwise thiobenzoic S-acid (0.66 ml) under ice-cooling. After stirring under the same condition for 30 minutes, this solution was added to a solution of (2S,4R)-2-(carbamoylmethyl)thiomethyl-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.68 g) in N,N-dimethylformamide (20 ml) at ambient temperature. The mixture was stirred at 70-80 °C for 1 hour. The reaction mixture was poured into ice-water (50 ml) and extracted twice with ethyl acetate (50 ml). The organic layer was washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo to give a residue. The residue was chromatographed on silica gel (100 g) eluting with a mixture of dichloromethane and acetone (5:1,V/V). The fractions containing the desired compound were collected and evaporated in vacuo to give (2S,4S)-4-benzoylthio-2-(carbamoylmethyl)thiomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (0.87 g).

IR (Neat) : 1710 (sh), 1690-1660, 1610, 1525, 1350, 1210 cm^{-1}

NMR ($CDCl_3$, δ) : 2.40-3.15 (4H, m), 3.21 (2H, s), 3.75-4.50 (3H, m), 5.23 (2H, s), 7.20-7.75 (5H, m), 7.93 (2H, d, J = 8Hz), 8.23 (2H, d, J = 8Hz)

Preparation 7-1)

To a solution of (2S,4S)-4-benzoylthio-2-(difluoromethyl)thiomethyl-1-(4-nitrobenzyloxycarbonyl)-pyrrolidine (1.0 g) in a mixture of methanol (10 ml) and tetrahydrofuran (10 ml) was added 28% sodium methoxide-methanol solution (0.52 ml) under an atmosphere of nitrogen at 2-5 • C. The mixture was stirred at the same temperature for 30 minutes. To the reaction mixture was added glacial acetic acid (1 ml) and the mixture was concentrated under reduced pressure. The resulting residue was dissolved in ethyl acetate (50 ml) The solution was washed twice with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (80 g) eluting with a mixture of n-hexane and ethyl acetate (2:1,V/V). The fractions containing the desired compound were collected and concentrated under reduced pressure to give (2S,4S)-2-(difluoromethyl)-thiomethyl-4-mercapto-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (0.58 g).

IR (Neat) : 1710-1700, 1610, 1525, 1410, 1350, 1205 cm^{-1}

NMR ($CDCl_3$, δ) : 1.40-2.05 (5H, m), 2.35-2.75 (1H, m), 3.05-3.50 (4H, m), 3.85-4.40 (2H, m), 5.25 (2H, s), 6.80 (1H, t, J = 56Hz), 7.53 (2H, d, J = 8Hz), 8.25 (2H, d, J-8Hz)

EI Mass : 281 (M^+-97)

Preparation 7-2)

To a solution of (2S,4S)-4-benzoylthio-2-(carbamoylmethyl)thiomethyl-1-(4-nitrobenzyloxycarbonyl)-pyrrolidine (0.86 g) in methanol (20 ml) was added 28% sodium methoxide-methanol solution (0.44 ml) at 0-2 • C under an atmosphere of nitrogen. The mixture was stirred under the same condition for 30 minutes. To the reaction mixture was added glacial acetic acid (0.8 ml) and the mixture was concentrated under reduced pressure to give a residue. The residue was dissolved in ethyl acetate (50 ml). The solution was washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (100 g) eluting with a mixture of dichloromethane and acetone (5:1, V/V). The fractions containing the desired compound were collected and evaporated in vacuo to give (2S,4S)-2-(carbamoylmethyl)thimethyl-4-mercapto-1-(4-nitrolbenzyloxy carbonyl)pyrrolidine (0.47 g).

IR (Neat) : 1710, 1630, 1520, 1350, 1205 cm^{-1}

NMR ($CDCl_3$, δ) : 1.75-1.95 (3H, m), 2.45-2.85 (1H, m), 2.90-3.15 (2H, m), 3.21 (2H, s), 3.25-3.50 (2H, m), 3.85-4.30 (2H, m), 5.24 (2H, s), 7.55 (2H, d, J = 8Hz), 8.27 (2H, d, J = 8Hz)

Preparation 8

To a solution of (3S)-3-mercapto-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.36 g) in methanol (5 ml) was added 28% sodium methoxide-methanol solution (0.97 ml) under ice-cooling and the mixture was stirred at the same temperature for 10 minutes. This solution was added to a solution of (2S,4R)-4-t-butyldimethylsilyloxy-2-methanesulfonyloxymethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (2 g) in methanol (20 ml). The mixture was stirred at ambient temperature for 3 hours and then at 50 • - 60 • C for 5 hours. The reaction mixture was evaporated in vacuo to give a residue. The residue was dissolved in ethyl acetate (50 ml). The solution was washed with saturated aqueous sodium chloride, dried over magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (100 g) eluting with a mixture of n-hexane and ethyl acetate (2:1 v/v). The fractions containing the desired compound were collected and evaporated in vacuo to give (2S,4R)-4-t-butyldimethylsilyloxy-1-(4-nitrobenzyloxycarbonyl)-2-[{(3S)-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-3-ylthio}methyl] pyrrolidine (1.95 g).

IR (Neat) : 1715-1700, 1610, 1525, 1350, 1255 cm^{-1}

Preparation 9

To a solution of (2S,4R)-4-t-butyldimethylsilyloxy-1-(4-nitrobenzyloxycarbonyl)-2-[{(3S)-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-3-ylthio}methyl]pyrrolidine (1.94 g) in a mixture of methanol (20 ml) and tetrahydrofuran (20 ml) was added conc. hydrochloric acid (0.48 ml) at ambient temperature and the mixture was stirred at ambient temperature for 1 hour. The reaction mixture was evaporated in vacuo to give a residue. The residue was dissolved in ethyl acetat (50 ml) and the solution was washed thre times with saturated aqueous sodium hydrogen carbonate (50 ml) and saturated aqueous sodium chloride (20 ml) successively, dried over magnesium sulfate, and evaporated in vacuo. The resulting residue was chromatographed on silica gel (100 g) eluting with a mixture of dichloromethane and acetone (5:1 v/v) to

give (2S,4R)-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)-2-[{(3S)-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-3-ylthio}-methyl]pyrrolidine (1.10 g).

IR (Neat) : 1710-1685, 1610, 1525, 1345 cm^{-1}

NMR ($CDCl_3$, δ) : 1.65-2.40 (4H, m), 2.70-3.15 (2H, m), 3.15-3.90 (7H, m), 4.10-4.40 (1H, m), 4.40-5.60 (1H, m), 5.22 (4H, s), 7.56 (4H, d, J = 8Hz), 8.23 (4H, d, J = 8Hz)

Preparation 10

To a suspension of sodium borohydride (0.20 g) in tetrahydrofuran (10 ml) was added dropwise boron trifluoride etherate (2.25 ml) under ice-cooling. The mixture was stirred at the same temperature for 10 minutes. To the solution obtained above was added (2S,4R)-2-(carbamoylmethylthio)methyl-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (0.92 g) under ice-cooling. The mixture was stirred at ambient temperature for 3 hours. To the reaction mixture was added methanol (5 ml) and the mixture was evaporated in vacuo. The resulting residue was dissolved in a mixture of methanol (10 ml) and conc. hydrochloric acid (1 ml). The solution was allowed to stand overnight at ambient temperature. The reaction mixture was evaporated in vacuo to give (2S,4R)-2-(2-aminoethylthio)methyl-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)-pyrrolidine hydrochloride. The compound obtained above was dissolved in a mixture of ethyl acetate (40 ml) and saturated aqueous sodium hydrogen carbonate (80 ml). The separated aqueous layer was washed with ethyl acetate (40 ml). To the aqueous layer was added ethyl acetate (40 ml) and the mixture was cooled in ice-bath. To the mixture obtained above was added dropwise a solution of 4-nitrobenzyloxycarbonyl chloride (0.54 g) in tetrahydrofuran (10 ml) with stirring under ice-cooling, while the pH was kept between 8 and 9 with 1N aqueous sodium hydroxide. The solution was stirred under the same condition for additional 1 hour. The organic layer of the reaction mixture was separated, washed with saturated aqueous sodium chloride, dried over magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (50 g) eluting with a mixture of chloroform and methanol (9:1 v/v). The fractions containing the desired compound were collected and concentrated under reduced pressure to give (2S,4R)-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)-2-[{2-(4-nitrobenzyloxycarbonylamino)ethylthio}methyl]pyrrolidine (1.01 g).

IR (Neat) : 1710-1700, 1690, 1610, 1530-1515, 1350 cm^{-1}

NMR ($CDCl_3$, δ) : 2.50-2.95 (3H, m), 3.20-3.70 (4H, m), 5.15-5.28 (4H, m), 7.53 (4H, br d, J = 8Hz), 8.23 (4H, d, J = 8Hz)

Preparation 11-1)

(2S,4S)-4-Benzoylthio-1-(4-nitorbenzyloxycarbonyl)-2-[{(3S)-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-3-ylthio}-methyl]pyrrolidine (0.75 g) was obtained by reacting (2S,4R)-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)-2-[{(3S)-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-3-ylthio}methyl]pyrrolidine (1.08 g) with thiobenzoic S-acid (0.34 ml) in substantially the same manner as that of Preparation 4.

NMR ($CDCl_3$, δ) : 1.75-2.40 (2H, m), 3.20-4.55 (9H, m), 5.27 (4H, s), 7.40-7.70 (7H, m), 7.85-8.10 (2H, m), 8.25 (4H, d, J = 8Hz)

Preparation 11-2)

(2S,4S)-4-Benzoylthio-1-(4-nitrobenzyloxycarbonyl)-2-[{2-(4-nitrobenzyloxycarbonyl))-ethylthio}methylpyrrolidine (0.89 g) was obtained by reacting (2S,4R)-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)-2-[{2-(4-nitrobenzyloxycarbonylamino)ethylthio}methyl]pyrrolidine (1.0 g) with thiobenzoic S-acid (0.33 ml) in substantially the same manner as that of Preparation 4.

IR (Neat) : 1725-1705, 1680-1660, 1610, 1530-1510 cm^{-1}

NMR ($CDCl_3$, δ) : 2.40-3.10 (5H, m), 3.15-3.60 (2H, m), 5.15-5.35 (4H, m), 7.35-7.70 (7H, m), 7.75-8.05 (2H, m), 8.22 (4H, br d, J = 8Hz)

Preparation 12-1)

(2S,4S)-4-Mercapto-1-(4-nitrobenzyloxycarbonyl)-2-[{(3S)-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-3-ylthio}-methyl]pyrrolidine (0.42 g) was obtained by reacting (2S,4S)-4-benzoylthio-1-(4-nitrobenzyloxycarbonyl)-2-[{(3S)-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-3-ylthio}-methyl]pyrrolidine (0.73 g) with 28% sodium methoxid -methanol solution (0.27 ml) in substantially the same manner as that of Preparation 7-1).

IR (Neat) : 1720-1690, 1605, 1530-1515 cm^{-1}

NMR ($CDCl_3$, δ) : 3.90-4.20 (2H, m), 5.25 (4H, s), 7.55 (4H, d, J = 8Hz), 8.26 (4H, d, J = 8Hz)

Preparation 12-2)

(2S,4S)-4-Mercapto-1-(4-nitrobenzyloxycarbonyl)-2-[{2-(4-nitrobenzyloxycarbonylamino)-ethylthio}methyl]pyrrolidine (0.48 g) was obtained by reacting (2S,4S)-4-benzoylthio-1-(4-nitrobenzyloxycarbonyl)-2-[{2-(4-nitrobenzyloxycarbonylamino)ethylthio}methyl]pyrrolidine (0.88 g) with 28% sodium methoxide-methanol solution (0.34 ml) in substantially the same manner as that of Preparation 7-1).

IR (Neat) : 1710-1700, 1610, 1530-1520, 1350 cm^{-1}

NMR ($CDCl_3$, δ) : 1.60-2.00 (2H, m), 2.30-3.65 (8H, m), 3.80-4.35 (2H, m), 5.20 (4H, s), 7.50 (4H, d, J = 8Hz), 8.21 (4H, d, J = 8Hz)

SI Mass : 551 (M^+), 369 (M^+-182)

Preparation 13

To a solution of sodium borohydride (0.78 g) in tetrahydrofuran (25 ml) was added dropwise boron trifluoride dimethyl etherate (8.78 ml) with stirring under ice-cooling and the solution was stirred at the same temperature for 10 minutes. To this solution was added (2S,4R)-2-(carbamoylmethyl)thiomethyl-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (2.53 g) and the mixture was stirred at ambient temperature for 4 hours. To the reaction mixture was added methanol (5 ml) and the mixture was filtered. The filtrate was evaporated in vacuo to give a residue. The residue was dissolved in methanol (30 ml). To the solution was added 10% hydrogen chloride-methanol solution (10 ml) and the mixture was allowed to stand overnight at ambient temperature. The reaction mixture was evaporated in vacuo to give a residue. The residue was dissolved in a mixture of tetrahydrofuran (30 ml) and water (15 ml). To the solution was added a solution of potassium cyanate (3.83 g) in water (10 ml) and the mixture was stirred at 50° - 60°C for 30 minutes. The reaction mixture was evaporated in vacuo. The resulting residue was chromatographed on silica gel (100 g) eluting with a mixture of chloroform and methanol (9:1, v/v). The fractions containing the desired compound were collected and evaporated in vacuo to give (2S,4R)-2-(2-ureidoethyl)thiomethyl-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.73 g).

IR (Neat): 1690-1660, 1610, 1530, 1350 cm^{-1}

NMR ($CDCl_3$, δ): 1.80-2.38 (2H, m), 2.46-3.78 (8H, m), 4.00-4.60 (3H, m), 5.00 (2H, s), 5.23 (2H, s), 5.94 (1H, t, J = 6Hz), 7.56 (2H, d, J = 8Hz), 8.23 (2H, d, J = 8Hz)

Preparation 14

To a solution of (2S,4R)-2-aminomethyl-4-t-butyldimethylsilyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (5 g) and triethylamine (1.87 ml) in N,N-dimethylformamide (50 ml) was dropwise added ethyl bromoacetate (1.49 ml) at ambient temperature with stirring. The mixture was stirred at 40 °C for 30 minutes and then allowed to stand at ambient temperature for 6 hours. The reaction mixture was poured into saturated aqueous sodium chloride (100 ml) and extracted twice with ethyl acetate (100 ml). The extract was washed with saturated aqueous sodium chloride, dried over magnesium sulfate and evaporated in vacuo. The resulting residue was subjected to a column chromatography on silica gel (100 g) eluting with a mixture of dichloromethane and acetone (20:1 v/v). The fractions containing the desired compound were collected and evaporated in vacuo to give (2S,4R)-4-t-butyldimethylsilyloxy-2-[(ethoxycarbonylmethyl)aminomethyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (3.52 g).

IR (Neat) : 1740, 1710, 1610, 1530, 1350, 1260 cm^{-1}

NMR ($CDCl_3$, δ) : 0.06 (6H, s), 0.83 (9H, s), 1.24 (3H, t, J = 7Hz), 1.88-2.20 (2H, m), 5.24 (2H, s) 7.40-7.65 (2H, m), 8.23 (2H, d, J = 8Hz)

Preparation 15

To a solution of (2S,4R)-4-t-butyldimethylsilyloxy-2-[(ethoxycarbonylmethyl)aminomethyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (3.51 g) and triethylamine (1.28 ml) in tetrahydrofuran (35 ml) was dropwise added a solution of 4-nitrobenzyloxycarbonyl chloride (1.60 g) in tetrahydrofuran (5 ml) under ice-cooling. The mixture was stirred at the same temperature for 1 hour. The reaction mixture was concentrated under reduced pr ssure. The resulting residue was dissolved in ethyl acetate (100 ml) and the solution was washed with saturated aqueous sodium chloride, dried over magnesium sulfate, and evaporated in vacuo. The resulting residue was subjected to a column chromatography on silica gel (100 g) eluting with a mixture of dichloromethane and acetone (40:1 v/v). The fractions containing the desired compound were collected and evaporated in vacuo to give (2S,4R)-4-t-butyldimethylsilyloxy-2-[N-ethoxycarbonylmethyl-N-(4-nitroben-

zyloxycarbonyl)]aminomethyl-1-(4-nitro-benzyloxycarbonyl)pyrrolidine (3.32 g).

IR (Neat) : 1750, 1710-1700, 1610, 1525, 1350, 1255 cm^{-1}

NMR ($CDCl_3$, δ) : 0.03 (6H, s), 0.83 (9H, s), 1.10-1.35 (3H, m), 1.80-2.20 (2H, m), 3.35-3.75 (4H, m), 3.75-4.55 (6H, m), 5.20 (4H, s), 7.36-7.66 (4H, m) 8.22 (4H, d, J = 8Hz)

Preparation 16

To a solution of (2S,4R)-4-t-butyldimethylsilyloxy-2-[N-ethoxycarbonylmethyl-N-(4-nitrobenzyloxycarbonyl)]aminomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (3.31 g) in methanol (20 ml) was added 3N ammonia in mathanol solution (16.4 ml) at ambient temperature. The mixture was allowed to stand overnight at the same temperature. The reaction mixture was evaporated in vacuo. The resulting residue was dissolved in ethyl acetate (60 ml) and the solution was washed with saturated aqueous sodium chloride, dried over magnesium sulfate and evaporated in vacuo to give (2S,4R)-4-t-butyldimethylsilyloxy-2-[N-carbamoylmethyl-N-(4-nitrobenzyloxycarbonyl)]aminomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (3.32 g).

IR (Neat) : 1710-1700, 1610, 1530, 1350, 1250 cm^{-1}

NMR ($CDCl_3$, δ) : 0.03 (6H, s), 0.83 (9H, s), 1.80-2.10 (2H, m), 5.22 (4H, s), 7.36-7.60 (4H, m), 8.22 (4H, d, J = 8Hz)

Preparation 17

(2S,4R)-2-(N-Carbamoylmethyl-N-(4-nitrobenzyloxycarbonyl]aminomethyl-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (2.30 g) was obtained by reacting (2S,4R)-4-t-butyldimethylsilyloxy-2-[N-carbamoylmethyl-N-(4-nitrobenzyloxycarbonyl)]aminomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (3.31 g) with conc. hydrochloric acid (0.85 ml) in substantially the same manner as that of Preparation 9.

IR (Neat) : 1710-1690, 1610, 1530-1520, 1350 cm^{-1}

NMR ($CDCl_3$, δ) : 1.90-2.28 (2H, m), 3.35-4.60 (10H, m) 5.20 (4H, s), 7.43 (2H, d, J = 8Hz), 7.51 (2H, d, J = 8Hz), 8.21 (4H, d, J = 8Hz)

Preparation 18-1)

(2S,4S)-4-Benzoylthio-2-[N-carbamoylmethyl-N-(4-nitrobenzyloxycarbonyl)]aminomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (2.43 g) was obtained by reacting (2S,4R)-2-[N-carbamoylmethyl-N-(4-nitrobenzyloxycarbonyl)]aminomethyl-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (2.29 g) with triphenylphosphine (1.70 g) and diethyl azodicarboxylate (1.02 ml), and then with thiobenzoic S-acid (0.76 ml) in substantially the same manner as that of Preparation 4.

NMR ($CDCl_3$, δ): 1.85-2.32 (1H, m), 2.35-2.85 (1H, m), 5.20 (4H, s), 7.33-7.65 (7H, m), 7.85-8.00 (2H, m), 8.22 (4H, d, J = 8H)

Preparation 18-2)

(2S,4S)-4-Benzoylthio-2-(2-ureidoethyl)thiomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.87 g) was obtained by reacting (2S,4R)-2-(2-ureidoethyl)thiomethyl-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.71 g) with triphenylphospine (1.69 g) and diethyl azodicarboxylate (1.01 ml), and then with thiobenzoic S-acid (0.76 ml) in substantially the same manner as that of Preparation 4.

IR (Neat): 1710-1650, 1530-1515, 1350-1340 cm^{-1}

NMR ($CDCl_3$, δ): 1.60-2.25 (2H, m), 2.40-3.60 (8H, m), 3.83-4.38 (3H, m), 4.45-4.80 (2H, m), 5.22 (2H, s), 5.35-5.65 (1H, m), 7.33-7.76 (5H, m), 7.95 (2H, dd, J = 7, 2Hz), 8.24 (2H, d, J = 8Hz)

Preparation 19-1)

(2S,4S)-2-[N-Carbamoylmethyl-N-(4-nitrobenzyloxycarbonyl)]aminomethyl-4-mercapto-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.46 g) was obtained by reacting (2S,4S)-4-benzoylthio-2-[N-carbamoylmethyl-N-(4-nitrobenzyloxycarbonyl)]aminomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (2.42 g) with 28% sodium methoxide-methanol solution (0.93 ml) in substantially the sam manner as that of Preparation 7-1).

IR (Neat): 1710-1790, 1610, 1530-1520 cm^{-1}

NMR ($CDCl_3$, δ): 1.63-2.00 (2H, m), 2.27-2.76 (1H, m), 3.00-3.50 (2H, m), 5.21 (4H, s), 7.33-7.66 (4H,

m), 8.22 (4H, d, J = 8Hz)

Preparation 19-2)

(2S,4S)-2-(2-Ureidoethyl)thiomethyl-4-mercapto-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.07 g) was obtained by reacting (2S,4S)-4-benzoylthio-2-(2-ureidoethyl)thiomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.85 g) with 28% sodium methoxide-methanol solution (0.89 ml) in substantially the same manner as that of Preparation 7-1).

IR (Neat): 1715-1655, 1610, 1530, 1350 cm^{-1}

NMR ($CDCl_3$, δ): 1.60-2.20 (2H, m), 2.40-3.70 (8H, m), 3.75-4.40 (2H, m), 4.60-4.90 (2H, m), 5.23 (2H, s), 5.30-5.60 (1H, m), 7.53 (2H, d, J = 8Hz), 8.25 (2H, d, J = 8Hz)

Preparation 20-1)

A mixture of (2S,4R)-4-t-butyldimethylsilyloxy-2-hydroxymethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (10.0 g), methanol (100 ml) and 20% palladium hydroxide on carbon (0.5 g) was stirred under atmospheric pressure of hydrogen at ambient temperature for 3 hours. The catalyst was filtered off and the filtrate was concentrated under reduced pressure to give a syrup. To a solution of the syrup in a mixture of tetrahydrofuran (100 ml) and water (100 ml) was dropwise added a solution of chloroacetyl chloride (5.0 ml) in tetrahydrofuran (10 ml) under ice-cooling with stirring, keeping the pH between 8-9 with 4N aqueous sodium hydroxide. The mixture was stirred at the same condition for 2 hours and extracted with a mixture of ethyl acetate and tetrahydrofuran (1:1 V/V) (100 ml x 5). The solution d over magnesium sulfate and concentrated under reduced pressure to give a syrup. The syrup was subjected to a column chromatography on silica gel (200 g) and eluted with a mixture of methanol and dichloromethane (1:99 V/V) to give (2S,4R)-4-t-butyldimethylsilyloxy-1-chloroacetyl-2-(hydroxymethyl)pyrrolidine (4.22 g).

IR (Neat) : 3400, 1660-1630 cm^{-1}

NMR ($CDCl_3$, δ) : 1.10 (6H, s), 1.90 (9H, s), 1.5-2.3 (3H, m), 3.3-3.9 (5H, m), 4.03 (2H, s), 4.1-4.5 (3H, m)

Preparation 20-2)

(2S,4R)-1-(2-Bromo-2-methylpropionyl)-4-t-butyldimethylsilyloxy-2-(hydroxymethyl)pyrrolidine (3.70 g) was obtained by reacting (2S,4R)-4-t-butyldimethylsilyloxy-2-(hydroxymethyl)pyrrolidine (3.00 g) with 2-bromo-2-methylpropionyl bromide (1.95 ml) in substantially the same manner as that of Preparation 20-1).

mp : 77-80 • C

IR (Nujol) : 1620 cm^{-1}

NMR ($CDCl_3$, δ) : 0.10 (6H, s), 0.90 (9H, s), 2.00 (6H, s)

Preparation 21-1)

A solution of (2S,4R)-4-t-butyldimethylsilyloxy-1-chloroacetyl-2-(hydroxymethyl)pyrrolidine (4.20 g) in tetrahydrofuran (20 ml) was dropwise added to a suspension of sodium hydride (62.8 % in oil suspension) (0.55 g) in tetrahydrofuran (60 ml) at 20-30 • C and the mixture was stirred at 25-30 • C for 3 hours. The mixture was concentrated under reduced pressure to give a syrup. A solution of the syrup in ethyl acetate (80 ml) was washed with water (100 ml), dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was subjected to a column chromatography on silica gel (30 g) and eluted with a mixture of methanol and chloroform (1:99 V/V) to give (6S,8R)-8-t-butyldimethylsilyloxy-2-oxo-1-aza-4-oxabicyclo[4.3.0]nonane (3.49 g).

mp : 81-82 • C

IR (Nujol) : 1650 cm^{-1}

NMR ($CDCl_3$, δ) : 1.10 (6H, s), 1.90 (9H, s), 1.3-1.6 (1H, m), 1.8-2.1 (1H, m), 3.1-3.5 (2H, m), 3.8-4.3 (5H, m), 4.4-4.6 (1H, m)

MS : 256 (M^+-15), 214

Preparation 21-2)

(6S,8R)-8-t-butyldimethylsilyloxy-3,3-dimethyl-2-oxo-1-aza-4-oxabicyclo[4.3.0]nonan (1.18 g) was obtained by reacting (2S,4R)-1-(2-bromo-2-methylpropionyl-4-t-butyldimethylsilyloxy-2-(hydroxymethyl)-

pyrrolidine (3.70 g) with sodium hydride in substantially the same manner as that of Preparation 21-1).

mp : 40-45 °C

IR (Nujol) : 1740 cm^{-1}

NMR ($CDCl_3$, δ) : 0.02 (6H, s), 0.85 (9H, s), 1.37 (3H, s), 1.43 (3H, s)

Preparation 22

A suspension of (6S,8R)-8-t-butyldimethylsilyloxy-2-oxo-1-aza-4-oxabicyclo[4.3.0]nonane (1.43 g) in 6N hydrochloric acid (14 ml) was heated for 3 hours under reflux. After cooling, the solution was washed with ethyl acetate (7 ml x 2) and concentrated under reduced pressure to give (2S,4R)-2-(carboxymethyloxymethyl)-4-hydroxypyrrolidine hydrochloride.

Preparation 23

To a solution of the compound obtained in Preparation 22 in a mixture of water (30 ml) and tetrahydrofuran (30 ml) was dropwise added a solution of 4-nitrobenzyloxycarbonyl chloride (1.36 g) in tetrahydrofuran (6 ml) under ice-cooling with stirring, keeping the pH between 8-9 with 4N aqueous sodium hydroxide. The mixture was stirred under the same condition for 2 hours, adjusted to pH 2.5 with 6N hydrochloric acid and extracted with ethyl acetate (50 ml x 2). The organic solution was combined, washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to give a syrup. The syrup was subjected to a column chromatography on silica gel (20 g) and eluted with a mixture of methanol and chloroform (3:97 V/V) to give (2S,4R)-2-(carboxymethyloxymethyl)-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.45 g).

IR (Neat) : 3600-3300, 1750-1680 cm^{-1}

NMR (DMSO-d_6, δ) : 1.8-2.2 (2H, m), 3.2-3.7 (4H, m), 3.98 (2H, s), 3.9-4.4 (2H, m), 5.20 (2H, s), 7.58 (2H, d, J = 8.5Hz), 8.18 (2H, d, J = 8.5Hz)

Preparation 24-1)

A solution of (6S,8R)-8-t-butyldimethylsilyloxy-2-oxo-1-aza-4-oxabicyclo[4.3.0]nonane (20.0 g) in 6N hydrochloric acid (200 ml) was heated for 3 hours under reflux. After cooling, the solution was washed with ethyl acetate (100 ml) and concentrated under reduced pressure to give (2S,4R)-2-carboxymethyloxymethyl-4-hydroxypyrrolidine. The compound obtained above was dissolved in a mixture of tetrahydrofuran (100 ml) and water (100 ml). To the solution was dropwise added a solution of benzyloxycarbonyl chloride (11.55 ml) in tetrahydrofuran (20 ml) under ice-cooling with stirring, keeping the pH between 8-9 with 4N aqueous sodium hydroxide. The mixture was stirred at the same condition for 1 hour and washed with ethyl acetate (100 ml x 2). The aqueous solution was adjusted to pH 2 with 6N hydrochloric acid and ethyl acetate (150 ml) was added thereto. The organic layer was separated, washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to give (2S,4R)-1-benzyloxycarbonyl-2-carboxymethyloxymethyl-4-hydroxypyrrolidine (19.95 g).

IR ($CHCl_3$) : 3450-3050, 1750-1660 cm^{-1}

NMR ($CDCl_3$, δ) : 1.8-2.3 (2H, m), 3.4-3.9 (4H, m), 3.9-4.3 (3H, m), 4.3-4.6 (1H, m), 5.13 (2H, s), 7.34 (5H, s)

Preparation 24-2)

(2S,4R)-2-(1-Carboxy-1-methylethyl)oxymethyl-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (0.85 g) was obtained by reacting (6S,8R)-8-t-butyldimethylsilyloxy-3,3-dimethyl-2-oxo-1-aza-4-oxabicyclo[4.3.0]-nonane (1.15 g) with hydrochloric acid and 4-nitrobenzyloxycarbonyl chloride successively in substantially the same manners as those of Preparations 22 and 23.

IR (Neat) : 1710-1675 cm^{-1}

NMR ($CDCl_3$, δ) : 1.39 (3H, s), 1.41 (3H, s), 1.95-2.20 (2H, m), 5.23 (2H, m), 7.48 (2H, d, J = 8.5Hz), 8.19 (2H, d, J = 8.5Hz)

Preparation 25-1)

A solution of methanesulfonyl chlorid (0.62 ml) in dichloromethane (2 ml) was dropwise added to a solution of (2S,4R)-2-(carboxymethyloxymethyl)-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.42 g)

and triethylamine (1.4 ml) in dichloromethane (14 ml) at 0 - 5 °C, and the mixture was stirred at the sar temperature for 1 hour. The mixtur was poured into water (50 ml), adjusted to pH 2.5 with 6N hydrochlo acid and extracted with dichlorom thane (50 ml x 2). The organic layer was washed with brine, dried ov magnesium sulfate and concentrated under reduced pressure to give a syrup. The syrup was subjected to column chromatography on silica gel (20 g) and eluted with a mixture of methanol and chloroform (1:99 V/ to give (2S,4R)-2-(carboxymethyloxymethyl)-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidir (1.30 g).

IR ($CHCl_3$) : 1750, 1705 cm^{-1}

NMR ($CDCl_3$, δ) : 2.3-2.5 (2H, m), 3.03 (3H, s), 3.5-4.4 (5H, m), 4.08 (2H, s), 5.22 (2H, s), 5.2-5.4 (1H m), 5.8-6.2 (1H, m), 7.48 (2H, d, J = 8.5Hz), 8.19 (2H, d, J = 8.5Hz)

Preparation 25-2)

A solution of methanesulfonyl chloride (10 ml) in tetrahydrofuran (20 ml) was dropwise added to a solution of (2S,4R)-1-benzyloxycarbonyl-2-carboxymethyloxymethyl-4-hydroxypyrrolidine (19.95 g) and triethylamine (27 ml) in tetrahydrofuran (200 ml) at -10 ~ -5 °C and the mixture was stirred at the same temperature for 1 hour. The mixture was poured into water (200 ml), adjusted to pH 2.5 with 6N hydrochloric acid and extracted with ethyl acetate (150 ml x 2). The organic layer was washed with brine (200 ml x 2), dried over magnesium sulfate and concentrated under reduced pressure to give (2S,4R)-1-benzyloxycarbonyl-2-carboxymethyloxymethyl-4-methanesulfonyloxypyrrolidine (24.85 g).

IR (Neat) : 3500-3100, 1755-1650 cm^{-1}

Preparation 26-1)

A solution of isobutyl chloroformate (0.60 g) in tetrahydrofuran (1 ml) was dropwise added to a solution of (2S,4R)-2-(carboxymethyloxymethyl)-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.28 g) and triethylamine (0.82 ml) in tetrahydrofuran (13 ml) at -10 ~ -5 °C, and the mixture was stirred at the same temperature for 30 minutes. The mixture was dropwise added to concentrated ammonia water (10 ml) at 0 - 5 °C and the solution was stirred at the same temperature for 1 hour. The mixture was poured into water (50 ml) and extracted with chloroform (50 ml). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to give a syrup. The syrup was subjected to a column chromatography on silica gel (25 g) and eluted with a mixture of methanol and chloroform (2:98 V/V) to give (2S,4R)-2-(carbamoylmethyloxymethyl)-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.00 g).

IR (Neat) : 1710-1670 cm^{-1}

NMR ($CDCl_3$, δ) : 2.2-2.6 (2H, m), 3.06 (3H, s), 3.5-4.5 (7H, m), 3.98 (2H, s), 5.2-5.5 (1H, m), 5.29 (1H, m), 7.55 (2H, d, J = 8.5Hz), 8.28 (2H, d, J = 8.5Hz)

Preparation 26-2)

To a solution of (2S,4R)-1-benzyloxycarbonyl-2-carboxymethyloxymethyl-4-methanesulfonyloxypyrrolidine (3.80 g) in benzene (19 ml) was added thionyl chloride (0.90 ml) with stirring at ambient temperature and the mixture was stirred at the same temperature for one hour. To the mixture were added urea (1.80 g) and concentrated sulfuric acid (0.05 ml) successively. The mixture was heated under reflux for 5 hours. The reaction mixture was poured into ice-water (100 ml) and extracted with ethyl acetate (100 ml). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to give a syrup. The syrup was subjected to a column chromatography on silica gel (100 g) and eluted with a mixture of methanol and chloroform (1:99 V/V) to give (2S,4R)-1-benzyloxycarbonyl-4-methanesulfonyloxy-2-[(ureidocarbonylmethyl)oxymethyl]pyrrolidine (1.85 g).

mp : 120-122 °C

IR (KBr) : 3500-3100, 1725-1685 cm^{-1}

NMR ($CDCl_3$, δ) : 3.00 (3H, s), 4.04 (2H, s), 5.17 (2H, s), 5.95 (1H, br s), 7.38 (5H, s), 8.03 (1H, br s), 8.85 (1H, br s)

EI MS : 429 (M^+), 298, 254

Preparation 27

A solution of methanesulfonyl chloride (0.4 ml) in tetrahydrofuran (2 ml) was dropwise added to a solution of (2S,4R)-2-(1-carboxy-1-methylethyl)oxymethyl-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (0.84 g) and triethylamine (1 ml) in tetrahydrofuran (8 ml) at -10 ~ -5 °C and the mixture was stirred at the same condition for 30 minutes. The mixture was dropwise added to a 10% solution (20 ml) of ammonia in ethanol and the mixture was stirred at the same temperature for 1 hour. The mixture was concentrated under reduced pressure to give a residue. The residue was dissolved in ethyl acetate (50 ml), washed with water (50 ml), dried over magnesium sulfate and concentrated under reduced pressure to give a syrup. The syrup was subjected to a column chromatography on silica gel (20 g) and eluted with a mixture of methanol and chloroform (1:99 V/V) to give (2S,4R)-2-(1-carbamoyl-1-methylethyl)oxymethyl-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.01 g).

IR ($CHCl_3$) : 1710-1685 cm^{-1}

NMR ($CDCl_3$, δ) : 1.37 (6H, s), 3.05 (3H, s), 5.24 (2H, s), 7.51 (2H, d, J = 8.5Hz), 8.23 (2H, d, J = 8.5Hz)

Preparation 28

To (2S,4R)-2-(carbamoylmethyl)oxymethyl-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.75 g) was added N,N-dimethylformamide dimethylacetal (1.75 ml) and the mixture was stirred at 70 °C for 3 hours. The mixture was poured into ethyl acetate, washed in turn with water and brine, and evaporated in vacuo. The oily residue was dissolved in acetic acid (30 ml) and to this solution was added hydrazine hydrate (0.32 ml) at room temperature. After stirring at the same temperature for 2 hours, the mixture was poured into a mixture of water and ethyl acetate. The organic layer was washed in turn with saturated aqueous sodium bicarbonate and brine, dried over magnesium sulfate and evaporated in vacuo. The oily residue was subjected to a column chromatography on silica gel eluting with a mixture of acetone and dichloromethane (1:4, V/V) to give (2S,4R)-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)-2-[(2H-1,2,4-triazol-3-ylmethyl)oxymethyl]pyrrolidine (1.47 g).

IR (CH_2Cl_2) : 1690-1710, 1610 cm^{-1}

NMR ($CDCl_3$, δ) : 3.07 (3H, s), 4.70 (2H, s), 5.1-5.4 (3H, m), 7.4-7.7 (2H, d, J = 9Hz), 8.21 (2H, d, J = 9Hz), 8.09 (1H, s)

Preparation 29

A solution of (2S,4R)-1-benzyloxycarbonyl-4-methanesulfonyloxy-2-[(ureidocarbonylmethyl)oxymethyl]-pyrrolidine (3.00 g) in a mixture of methanol (30 ml) and tetrahydrofuran (60 ml) was hydrogenated under atmospheric pressure of hydrogen at ambient temperature for 5 hours in the presence of 20% palladium hydroxide on carbon (1 g). The catalyst was filtered off and the filtrate was concentrated under reduced pressure to give (2S,4R)-4-methanesulfonyloxy-2-[(ureidocarbonylmethyl)oxymethyl]pyrrolidine. To a solution of the compound obtained above in a mixture of tetrahydrofuran (20 ml) and water (20 ml) was dropwise added a solution of allyl chloroformate (0.82 ml) in tetrahydrofuran (2 ml) under ice-cooling with stirring, keeping the pH between 9-10 with 4N aqueous sodium hydroxide. The mixture was stirred at the same condition for 1 hour and extracted with ethyl acetate (50 ml). The organic layer was dried over magnesium sulfate and evaporated under reduced pressure to give a syrup. The syrup was subjected to a column chromatography on silica gel (15 g) and eluted with a mixture of methanol and chloroform (2:98 v/v) to give (2S,4R)-1-allyloxycarbonyl-4-methanesulfonyloxy-2-[(ureidocarbonylmethyl)oxymethyl]pyrrolidine (1.11 g).

IR (Neat) : 1720-1685 cm^{-1}

NMR ($CDCl_3$, δ) : 3.07 (3H, s), 4.10 (2H, s)

Preparation 30-1)

A solution of (2S,4R)-2-(carbamoylmethyl)oxymethyl-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (0.98 g) in dimethylformamide (2 ml) was added to a reaction mixture of thioacetic S-acid (0.25 ml) and sodium hydride (62.8% in oil suspension) (0.11 g) in dimethylformamide (10 ml) in a nitrogen stream and the mixture was heat d at 70-75 °C for 3 hours. Th mixture was poured into water (100 ml), extracted with ethyl acetate (50 ml x 3), dried over magnesium sulfate and concentrated under reduced pressure to give a syrup. The syrup was subjected to a column chromatography on silica gel (20 g) and eluted with a mixture of methanol and chloroform (1:99 v/v) to give (2S,4S)-4-acetylthio-2-

(carbamoylmethyl)oxymethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (0.72 g).

IR (Neat) : 1715-1670 cm^{-1}

NMR ($CDCl_3$, δ) : 2.33 (3H, s), 3.72 (2H, d, J = 5Hz), 3.97 (2H, s), 5.20 (2H, s), 7.45 (2H, d, J = 8.5Hz), 8.18 (2H, d, J = 8.5Hz)

Preparation 30-2)

(2S,4S)-4-Acetylthio-1-(4-nitrobenzyloxycarbonyl)-2-[(2H-1,2,4-triazol-3-ylmethyl)oxymethyl]pyrrolidine (1.18 g) was obtained by reacting (2S,4R)-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)-2-[{(2H-1,2,4-triazol-3-yl)methyl}oxymethyl]pyrrolidine (1.47 g) with thioacetic S-acid (0.36 ml) in substantially the same manner as that of Preparation 30-1).

IR (CH_2Cl_2) : 1690-1710, 1610 cm^{-1}

NMR ($CDCl_3$, δ) : 2.32 (3H, s), 3.1-3.4 (1H, m), 4.72 (2H, s), 5.24 (2H, s), 7.51 (2H, d, J = 9Hz), 8.09 (1H, s), 8.28 (2H, d, J = 9Hz)

Preparation 30-3)

(2S,4S)-4-Acetylthio-1-allyloxycarbonyl-2-[(ureidocarbonylmethyl)oxymethyl]pyrrolidine (0.60 g) was obtained by reacting (2S,4R)-1-allyloxycarbonyl-4-methanesulfonyloxy-2-[(ureidocarbonylmethyl)oxymethyl]-pyrrolidine (1.05 g) with thioacetic S-acid (0.44 ml) in substantially the same manner as that of Preparation 30-1).

IR (Neat) : 1730-1670 cm^{-1}

NMR ($CDCl_3$, δ) : 2.33 (3H, s), 4.06 (2H, s)

Preparation 30-4)

(2S,4S)-4-Acetylthio-2-(1-carbamoyl-1-methylethyl)oxymethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (0.84 g) was obtained by reacting (2S,4R)-2-(1-carbamoyl-1-methylethyl)oxymethyl-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (0.95 g) in substantially the same manner as that of Preparation 30-1).

IR (Neat) : 1710-1675 cm^{-1}

NMR ($CDCl_3$, δ) : 1.40 (6H, s), 2.37 (3H, s), 5.23 (2H, s), 7.51 (2H, d, J = 8.5Hz), 8.24 (2H, d, J = 8.5Hz)

Preparation 31-1)

To a solution of (2S,4S)-4-acetylthio-2-(carbamoylmethyl)oxymethyl-1-(4-nirobenzyloxycarbonyl)-pyrrolidine (0.80 g) in methanol (16 ml) was added sodium methoxide (28% solution in methanol (0.45 ml) at -10~-5 °C in a nitrogen stream and the mixture was stirred at the same condition for 0.5 hour. To the mixture was added glacial acetic acid (0.15 ml) at -10~0 °C. The mixture was concentrated under reduced pressure to give a residue. The residue was dissolved in ethyl acetate (40 ml). The solution was washed with water (40 ml), dried over magnesium sulfate and concentrated under reduced pressure to give a syrup. The syrup was subjected to a column chromatography on a silica gel (20 g) and eluted with a mixture of methanol and chloroform (1:99 v/v) to give (2S,4S)-2-(carbamoylmethyl)oxymethyl-4-mercapto-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (0.60 g).

IR (Neat) : 1710-1670 cm^{-1}

NMR ($CDCl_3$, δ) : 3.96 (2H, s), 5.20 (2H, s), 7.48 (2H, d, J = 8.5Hz), 8.20 (2H, d, J = 8Hz)

Preparation 31-2)

(2S,4S)-4-Mercapto-1-(4-nitrobenzyloxycarbonyl)-2-[(2H-1,2,4-triazol-3-yl)methyloxymethyl]pyrrolidine (1.0 g) was obtained by reacting (2S,4S)-4-acetylthio-1-(4-nitrobenzyloxycarbonyl)-2-[{(2H-1,2,4-triazol-3-yl)-methyl}oxymethy]pyrrolidine (1.18 g) with sodium methoxide (28% solution in methanol) (0.83 ml) in substantially the same manner as that of Preparation 31-1).

IR (CH_2Cl_2) : 1690-1710, 1610 cm^{-1}

NMR ($CDCl_3$, δ) : 4.72 (2H, s), 5.23 (2H, s), 7.52 (2H, d, J = 9Hz), 8.08 (1H, s), 8.27 (2H, d, J = 9Hz)

Preparation 31-3)

(2S,4S)-1-Allyloxycarbonyl-4-mercapto-2-(ureidocarbonylmethyl)oxymethylpyrrolidine (0.36 g) was obtained by reacting (2S,4S)-4-acetylthio-1-allyloxycarbonyl-2-[(ureidocarbonylmethyl)oxymethyl]pyrrolidine (0.58 g) with sodium methoxide (28% solution in methanol) (0.36 ml) in substantially the same manner as that of Preparation 31-1).

IR (Neat) : 1720-1670 cm^{-1}

NMR ($CDCl_3$, δ) : 4.10 (2H, s)

Preparation 31-4)

(2S,4S)-2-(1-carbamoyl-1-methylethyl)oxymethyl-4-mercapto-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (0.65 g) was obtained by reacting (2S,4S)-4-acetylthio-2-(1-carbamoyl-1-methylethyl)oxymethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (0.83 g) in substantially the same manner as that of Preparation 31-1).

IR (Neat) : 1705-1675 cm^{-1}

NMR ($CDCl_3$, δ) : 1.39 (6H, s), 3.66 (2H, d, J = 4.5Hz), 3.9-4.3 (2H, m), 5.23 (2H, s), 7.52 (2H, d, J = 8.5Hz), 8.25 (2H, d, J = 8.5Hz)

Preparation 32

1) To a suspension of sodium hydride (62.8 % suspension in oil) (0.38 g) in N,N-dimethylformamide (12 ml) was added 5-mercapto-1-methyl-1H-tetrazole (1.14 g) under ice-cooling. The mixture was stirred at the same temperature for 30 minutes. This solution was added dropwise to a solution of (2S,4R)-4-t-butyldimethylsilyloxy-2-methanesulfonyloxymethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (3.0 g) in N,N-dimethylformamide (60 ml) under ice-cooling. The mixture was stirred at 60-70 °C for 2 hours. The reaction mixture was poured into ice-water (200 ml) and extracted 3 times with ethyl acetate (100 ml). The extracts were combined, washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (100 g) eluting with a mixture of dichloromethane and acetone (40:1, V/V). The fractions containing the desired compound were collected and concentrated under reduced pressure to give (2S,4R)-4-t-butyldimethylsilyloxy-2-(1-methyl-1H-tetrazol-5-yl)thiomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.68 g).

IR (Neat) : 1710-1700, 1610, 1530-1520, 1350, 1260 cm^{-1}

NMR ($CDCl_3$, δ) : 0.07 (6H, s), 0.86 (9H, s), 1.90-2.15 (2H, m), 3.40-3.60 (2H, m), 3.60-3.85 (2H, m), 3.83 (3H, s), 4.25-4.55 (2H, m), 5.15-5.35 (2H, m), 7.53 (2H, br. d, J = 8Hz), 8.23 (2H, d, J = 8Hz)

2) (2S,4R)-4-t-Butyldimethylsilyloxy-1-(4-nitrobenzyloxycarbonyl)-2-(1,3,4-thiadiazol-2-yl-thiomethyl)-pyrrolidine (2.41 g) was obtained by reacting (2S,4R)-4-t-butyldimethylsilyloxy-2-methanesulfonyloxymethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (3.0 g) with 2-mercapto-1,3,4-thiadiazole (2.32 g) in substantially the same manner as that of Preparation 32-1).

IR (Neat) : 1705, 1610, 1525, 1350, 1260 cm^{-1}

NMR ($CDCl_3$, δ) : 0.06 (6H, s), 0.82 (9H, s), 1.56 (1H, s), 1.93-2.22 (2H, m), 3.43-3.63 (2H, m), 3.66-3.95 (2H, m), 4.30-4.65 (2H , m), 5.25 (2H, br. s), 7.52 (2H, br. d, J = 8Hz), 8.21 (2H, d, J = 8Hz), 8.98 (1H, s)

3) (2S,4R)-4-t-Butyldimethylsilyloxy-2-[1-{2-(N,N-dimethylamino)ethyl}-1H-tetrazol-5-yl]thiomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (2.55 g) was obtained by reacting (2S,4R)-4-t-butyldimethylsilyloxy-2-methanesulfonyloxymethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (3.0 g) with 1-[2-(N,N-dimethylamino)-ethyl]-5-mercapto-1H-tetrazole (2.28 g) in substantially the same manner as that of Preparation 32-1).

IR (Neat) : 1710, 1678, 1610, 1528, 1405, 1260 cm^{-1}

NMR ($CDCl_3$, δ) : 0.04 (6H, s), 0.83 (9H, s), 1.88-2.21 (2H, m), 2.25 (6H, s), 3.45-3.64 (2H, m), 3.68-3.91 (2H, m), 4.17-4.60 (4H, m), 5.21-5.36 (2H, m), 7.55 (2H, br. d, J = 8Hz), 8.62 (2H, d, J = 8Hz)

4) (2S,4R)-4-t-Butyldimethylsilyloxy-1-(4-nitrobenzyloxycarbonyl)-2-(pyridin-4-ylthiomethyl)pyrrolidine (2.59 g) was obtained by reacting (2S,4R)-4-t-butyldimethylsilyloxy-2-mesulfonyloxymethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (3.5 g) with 4-mercaptopyridine (1.28 ml) in substantially the same manner as that of Preparation 32-1).

IR (Neat) : 1710-1700, 1610, 1580, 1525, 1350, 1260 cm^{-1}

NMR ($CDCl_3$, δ) : 0.06 (9H, s), 0.86 (3H, s), 1.90-2.25 (4H, m), 2.80-3.30 (1H, m), 3.35-3.65 (3H, m), 4.10-4.65 (2H, m), 5.25 (2H, br. s), 7.20-7.75 (4H, m), 8.15-8.55 (4H, m)

Preparation 33

1) To a solution of (2S,4R)-4-t-butyldimethylsilyloxy-2-(1-methyl-1H-tetrazol-5-yl)thiomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.67 g) in methanol (30 ml) was added conc. hydrochloric acid (0.82 ml) at ambient temperature. After stirring at the same temperature for 1 hour, the reaction mixture was concentrated under reduced pressure. The resulting residue was dissolved in ethyl acetate (80 ml). The solution was washed with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride successively, dried over anhydrous magnesium sulfate, and evaporated in vacuo to give (2S,4R)-4-hydroxy-2-(1-methyl-1H-tetrazol-5-yl)thiomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.25 g).

IR (Neat) : 1710-1680, 1610, 1525, 1350 cm^{-1}

NMR ($CDCl_3$, δ) : 2.10-2.35 (3H, m), 3.50-3.90 (4H, m), 3.93 (3H, s), 4.30-4.70 (2H, m), 5.21 (2H, s), 7.56 (2H, d, J = 8Hz), 8.22 (2H, d, J = 8Hz)

Mass : 394 (M^+)

2) (2S,4R)-4-Hydroxy-1-(4-nitrobenzyloxycarbonyl)-2-(1,3,4-thiadiazol-2-ylthiomethyl)pyrrolidine (1.76 g) was obtained by reacting (2S,4R)-4-t-butyldimethylsilyloxy-1-(4-nitrobenzyloxycarbonyl)-2-(1,3,4-thiadiazol-2-ylthiomethyl)pyrrolidine (2.40 g) with conc. hydrochloric acid in substantially the same manner as that of Preparation 33-1).

IR (Neat) : 1710, 1690, 1610, 1520, 1350 cm^{-1}

NMR ($CDCl_3$, δ) : 2.06-2.34 (3H, m), 3.50-3.90 (4H, m), 4.33-4.73 (2H, m), 5.22 (2H, s), 7.53 (2H,br.d, J = 8Hz), 8.20 (2H, d, J = 8Hz), 9.86 (1H, s)

Mass : 396 (M^+)

3) (2S,4R)-2-[1-{2-(N,N-Dimethylamino)ethyl}-1H-tetrazol-5-yl]thiomethyl-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.83 g) was obtained by reacting (2S,4R)-4-t-butyldimethylsilyloxy-2-[1-{2-(N,N-dimethylamino)ethyl}-1H-tetrazol-5-yl]thiomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (2.54 g) with conc. hydrochloric acid in substantially the same manner as that of Preparation 33-1).

IR (Neat) : 1705, 1610, 1525, 1405, 1350 cm^{-1}

NMR ($CDCl_3$,δ) : 2.02-2.25 (1H, m), 2.26 (6H, s), 2.63-3.01 (2H, m), 3.53-3.95 (4H, m), 4.18-4.67 (4H, m), 5.25 (2H, s), 7.58 (2H,br.d, J = 8Hz), 8.63 (2H, d, J = 8Hz)

Mass : 451 (M^+)

4) (2S,4R)-4-Hydroxy-1-(4-nitrobenzyloxycarbonyl)-2-(pyridin-4-ylthiomethyl)pyrrolidine (1.98 g) was obtained by reacting (2S,4R)-4-t-butyldimethylsilyloxy-1-(4-nitrobenzyloxycarbonyl)-2-(pyridin-4-ylthiomethyl)pyrrolidine (2.57 g) with conc. hydrochloric acid (1.25 ml) in substantially the same manner as that of Preparation 33-1) .

IR (Neat) : 1700-1685, 1610, 1590, 1525, 1350 cm^{-1}

NMR ($CDCl_3$, δ) : 2.70-3.20 (3H, m), 3.35-3.85 (3H, m), 4.15-4.60 (2H, m), 5.21 (2H, s), 7.15-7.40 (2H, m), 7.48 (2H, d, J = 8Hz), 8.18 (2H, d, J = 8Hz), 8.20-8.45 (2H, m)

Mass : 389 (M^+), 265 (M^+-124)

Preparation 34

1) To a solution of (2S,4R)-4-hydroxy-2-(1-methyl-1H-tetrazol-5-yl)thiomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.23 g) and triphenylphosphine (1.23 g) in tetrahydrofuran (25 ml) was added dropwise a solution of diethyl azodicarboxylate (0.74 ml) in tetrahydrofuran (2 ml) under ice-cooling. After stirring at the same temperature for 30 minutes, to the solution was added thiobenzoic S-acid (0.55 ml) under ice-cooling. The mixture was stirred at the same temperature for 2 hours. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was dissolved in ethyl acetate (100 ml) and the solution was washed with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride successively, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The resulting residue was chromatographed on silica gel (100 g) eluting with a mixture of dichloromethane and acetone (19:1, V/V). The fractions containing the resired compound were collected and evaporated in vacuo to give (2S,4S)-4-benzoylthio-2-(1-methyl-1H-tetrazol-5-yl)thiomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.61 g).

IR (Neat) : 1710-1700, 1665, 1610, 1525, 1350, 1210 cm^{-1}

NMR ($CDCl_3$, δ) : 3.92 (3H, s), 5.92 (2H, s), 7.41-7.75 (5H, m), 7.83-8.08 (2H, m), 8.25 (2H, d, J = 8Hz)

2) (2S,4S)-4-Benzoylthio-1-(4-nitrobenzyloxycarbonyl)-2-(1,3,4-thiadiazol-2-ylthiomethyl)pyrrolidine (2.73 g) was obtained by reacting (2S,4R)-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)-2-(1,3,4-thiadiazol-2-yl-

thiomethyl)pyrrolidine (1.77 g) with triphenylphosphine (1.76 g), diethyl azodicarboxylate (1.05 ml) and thiobenzoic S-acid (0.79 ml) successively in substantially the same manner as that of Pr paration 34-1).

IR (Neat) : 1710-1660, 1610, 1530-1520, 1350 cm^{-1}

NMR ($CDCl_3$, δ) : 3.80-4.06 (2H, m), 5.27 (2H, s), 7.37-7.73 (5H, m), 7.82-8.05 (2H, m), 8.24 (2H, d, J = 8Hz), 9.01 (1H, s)

3) (2S,4S)-4-Benzoylthio-2-[1-{2-(N,N-dimethylamino)ethyl}-1H-tetrazol-5-yl]thiomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (2.68 g) was obtained by reacting (2S,4R)-2-[1-{2-(N,N-dimethylamino)ethyl}-1H-tetrazol-5-yl]thiomethyl-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.82 g) with triphenylphosphine (1.59 g), diethyl azodicarboxylate (0.95 ml), and thiobenzoic S-acid (0.98 ml) successively in substantially the same manner as that of Preparation 34-1).

IR (Neat) : 1710, 1670-1660, 1610, 1525, 1405, 1350 cm^{-1}

NMR ($CDCl_3$, δ) : 2.22 (3H, s), 2.66-2.96 (2H, m), 4.15-4.50 (4H, m), 5.26 (2H, s), 8.25 (2H, d, J = 8Hz)

4) (2S,4S)-4-Benzoylthio-1-(4-nitrobenzyloxycarbonyl)-2-(pyridin-4-ylthiomethyl)pyrrolidine (3.56 g) was obtained by reacting (2S,4R)-4-hydroxy-1-(4-nitrobenzyloxycarbonyl-2-(pyridin-4-ylthiomethyl)pyrrolidine (1.97 g) with triphenylphosphine (1.99 g), diethyl azodicarboxylate (1.19 ml) and thiobenzoic S-acid (0.89 ml) successively in substantially the same manner as that of Preparation 34-1).

IR (Nujol) : 1710, 1670, 1585, 1525, 1350 cm^{-1}

NMR ($CDCl_3$, δ) : 2.40-2.70 (2H, m), 4.10-4.45 (2H, m), 5.25 (2H, s), 8.15-8.60 (4H, m)

Preparation 35

1) To a solution of (2S,4S)-4-benzoylthio-2-(1-methyl-1H-tetrazol-5-yl)thiomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.60 g) in methanol (30 ml) was added sodium methoxide (28% solution in methanol) (0.78 ml) under ice-cooling. After stirring at the same temperature for 30 minutes, to this solution was added glacial acetic acid (1 ml). The mixture was concentrated under reduced pressure to give a residue. The residue was dissolved in ethyl acetate (100 ml). The solution was washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (100 g) eluting with a mixture of dichloromethane and acetone (20:1, V/V). The fractions containing the desired compound were collected and evaporated in vacuo to give (2S,4S)-4-mercapto-2-(1-methyl-1H-tetrazol-5-yl)thiomethyl-1-(4-nitrobenzyloxycarbonyl)-pyrrolidine (0.78 g).

mp : 144-145 °C

IR (Neat) : 1710-1690, 1610, 1520, 1350 cm^{-1}

NMR ($CDCl_3$, δ) : 1.63-1.93 (2H, m), 1.98-2.25 (1H, m), 2.52-3.03 (1H, m), 3.12-3.53 (2H, m), 3.65-3.95 (1H, m), 3.92 (3H, s), 4.02-4.54 (2H, m), 5.22 (2H, s), 7.56 (2H,br.d, J = 8Hz), 8.21 (2H, d, J = 8Hz)

Mass : 410 (M^+), 377 (M^+-33)

2) (2S,4S)-4-Mercapto-1-(4-nitrobenzyloxycarbonyl)-2-(1,3,4-thiadiazol-2-ylthiomethyl)pyrrolidine (1.74 g) was obtained by reacting (2S,4S)-4-benzoylthio-1-(4-nitrobenzyloxycarbonyl)-2-(1,3,4-thiadiazol-2-ylthiomethyl)pyrrolidine (2.71 g) with sodium methoxide in substantially the same manner as that of Preparation 35-1).

mp : 81-82 °C

IR (Nujol) : 1700, 1605, 1535 (sh), 1520, 1405, 1340 cm^{-1}

NMR ($CDCl_3$, δ) : 1.71-1.90 (1H, m), 1.90-2.23 (2H, m), 2.43-2.96 (1H, m), 3.03-3.60 (2H, m), 3.70-4.03 (2H, m), 5.25 (2H, s), 7.60 (2H, br. d, J = 8Hz), 8.23 (2H, d, J = 8Hz), 9.03 (1H, s)

Mass: 379 (M^+-34)

3) (2S,4S)-2-[1-{2-(N,N-Dimethylamino)ethyl}-1H-tetrazol-5-yl]thiomethyl-4-mercapto-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.13 g) was obtained by reacting (2S,4S)-4-benzoylthio-2-[1-{2-(N,N-dimethylamino)ethyl}-1H-tetrazol-5-yl]thiomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (2.66 g) with sodium methoxide in substantially the same manner as that of Preparation 35-1).

IR (Neat) : 1710-1700, 1610, 1525, 1405, 1350 cm^{-1}

NMR ($CDCl_3$, δ) : 2.28 (6H, s), 5.25 (2H, s), 8.24 (2H, d, J = 8Hz)

Mass : 467 (M^+-1)

4) (2S,4S)-4-Mercapto-1-(4-nitrobenzyloxycarbonyl)-2-(pyridin-4-ylthiomethyl)pyrrolidine (2.40 g) was obtained by reacting (2S,4S)-4-benzoylthio-1-(4-nitrobenzyloxycarbonyl)-2-(pyridin-4-ylthiomethyl)pyrrolidine (3.54 g) with sodium methoxide in substantially the same manner as that of Pr paration 35-1).

IR (Nujol) : 1690, 1580, 1525, 1350 cm^{-1}

NMR ($CDCl_3$, δ) : 1.65-2.20 (2H, m), 2.40-2.90 (1H, m), 3.05-3.50 (2H, m), 3.50-3.65 (1H, m), 3.80-

4.40 (3H, m), 5.25 (2H, s), 8.20 (2H, d, J = 8Hz), 8.36 (2H, br. d, J = 6Hz)
Mass : 405 (M^+), 281 (M^+-124)

Preparation36

To a solution of (2S,4R)-2-(carboxymethyloxymethyl)-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (2.4 g) in tetrahydrofuran (50 ml) was added triethyamine (1.6 ml). Isobutyl chloroformate (1.1 ml) was dropwise added to the mixture at -5 to -10 °C under nitrogen, followed by stirring for 30 minutes at the same temperature. The insoluble material was filtered off and the filtrate was added to a solution of sodium borohydride (0.70 g) in water (20 ml) at 0 °C. After stirring for 2 hours at the same temperature, acetic (3 ml) was added thereto. The reaction mixture was evaporated, diluted with ethyl acetate and washed successively with water, saturated sodium bicarbonate and brine. The dried organic layer was concentrated under reduced pressure, and the obtained syrup was subjected to a column chromatography on silica gel and eluted with a mixture of dichloromethane and acetone (4:1 v/v) to give (2S,4R)-2-(2-hydroxyethyloxymethyl)-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (2.1 g).

IR (CH_2Cl_2) : 3460, 1680-1720, 1605 cm^{-1}

NMR ($CDCl_3$, δ) : 2.1-2.5 (2H, m), 3.02 (3H, s), 3.4-4.0 (8H, m), 4.1-4.4 (1H, m), 5.2-5.5 (3H, m), 7.53 (2H, d, J = 8.5Hz), 8.27 (2H, d, J = 8.5Hz)

Preparation 37

(2S,4S)-4-Acetylthio-2-(2-hydroxyethyloxymethyl)-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.8 g) was obtained by reacting (2S,4R)-2-(2-hydroxyethyloxymethyl)-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (2.1 g) with thioacetic S-acid (0.54 ml) and sodium hydride (62.8% suspension in oil, 0.29 g) in substantially the same manner as that of Preparation 30-1).

IR (Neat) : 3350-3450, 1670-1720, 1605 cm^{-1}

NMR ($CDCl_3$, δ) : 1.8-2.7 (2H, m), 2.33 (3H, s), 3.28 (1H, m), 3.5-4.4 (9H, m), 5.27 (2H, s), 7.54 (2H, d, J = 9Hz), 8.29 (2H, d, J = 9Hz)

Preparation 38

To a solution of (2S,4S)-4-acetylthio-2-(2-hydroxyethyloxymethyl)-1-(4-nitrobenzyloxycarbonyl)-pyrrolidine (1.1 g) in acetonitrile (20 ml) was added chlorosulfonyl isocyanate(0.32 ml) at 0-5 °C and the mixture was stirred at 20-25 °C for 1 hour. Water (3 ml) was added to the solution at the same temperature and the mixture was stirred for 20 hours. After the solvent was evaporated, the residue was dissolved in ethyl acetate, washed with water, saturated sodium bicarbonate and brine successively. The dried organic layer was evaporated to give (2S,4S)-4-acetylthio-2-(2-carbamoyloxyethyloxymethyl)-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.19 g).

IR (Neat) : 3450, 3350, 1680-1730, 1605 cm^{-1}

NMR ($CDCl_3$, δ) : 2.32 (3H, s), 2.2-2.8 (2H, m), 3.0-3.4 (1H, m), 3.5-3.8 (4H, m), 3.8-4.3 (5H, m), 4.5-5.0 (2H, m), 5.22 (2H, s), 7.56 (2H, d, J = 9Hz) 8.29 (2H, d, J = 9Hz)

Preparation 39-1)

(2S,4S)-2-(2-Hydroxyethyloxymethyl)-4-mercapto-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (520 mg) was obtained by reacting (2S,4S)-4-acetylthio-2-(2-hydroxyethyloxymethyl)-1-(4-nitrobenzyloxycarbonyl)-pyrrolidine (640 mg) with a 28% solution of sodium methoxide in methanol (0.5 ml) in substantially the same manner as that of Preparation 31-1).

IR (Neat) : 3400, 1685-1710, 1605 cm^{-1}

NMR ($CDCl_3$, δ) : 3.1-3.4 (1H, m), 3.4-3.8 (6H, m), 3.9-4.3 (3H, m), 5.21 (1H, m), 7.52 (2H, d, J = 9Hz) 8.29 (2H, d, J = 9Hz)

Preparation 39-2)

(2S,4S)-2-(2-Carbamoyloxyethyloxymethyl)-4-mercapto-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (910 mg) was obtained by reacting (2S,4S)-4-acetylthio-2-(2-carbamoyloxy thyloxymethyl)-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.19 g) with a 28% solution of sodium methoxide in methanol (0.83 ml) in substantially the same manner as that of Preparation 31-1).

IR (Neat) : 3300-3400, 1670-1720, 1600 cm^{-1}

NMR ($CDCl_3$, δ) : 3.0-3.4 (2H, m), 3.5-3.8 (4H, m), 3.9-4.3 (4H, m), 5.22 (2H, s), 7.53 (2H, d, J=9Hz), 8.29 (2H, d, J=9Hz)

Preparation 40

To a solution of (2S,4R)-2-acetylthiomethyl-4-t-butyldimethylsilyloxy-1-(4-nitrobenzyloxycarbonyl)-pyrrolidine (1 g) in methanol (10 ml) was added 28% sodium methoxide-methanol solution (0.45 ml) with stirring under ice-cooling and the mixture was stirred at the same temperature for 10 minutes. To the reaction mixture was dropwise added epichlorohydrin (0.22 ml) and then the mixture was stirred at ambient temperature for 2 hours. The reaction mixture was evaporated in vacuo. The resulting residue was dissolved in ethyl acetate (40 ml) and the solution was washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and concentrated under reduced pressure.

The resulting residue was subjected to a column chromatography on silica gel (50 g) eluting with a mixture of n-hexane and ethyl acetate (2:1 v/v). The fractions containing the desired compound were collected and evaporated in vacuo to give (2S,4R)-4-t-butyldimethylsilyloxy-2-[(2,3-epoxypropyl)thiomethyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (0.61 g).

IR (Neat) : 1710, 1610, 1525, 1350, 1260 cm^{-1}

NMR ($CDCl_3$, δ) : 0.06 (6H, s), 0.86 (9H, s), 1.90-2.20 (2H, m), 2.45-3.30 (7H, m), 3.45-3.65 (2H, m), 4.10-4.60 (2H, m), 5.27 (2H, s), 7.55 (2H, d, J=9Hz), 8.37 (2H, d, J=9Hz)

Preparation 41

A solution of (2S, 4R)-4-t-butyldimethylsilyloxy-2-[(2,3-epoxypropyl)thiomethyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (2.59 g), sodium azide (0.52 g) and ammonium chloride (0.43 g) in N,N-dimethylformamide (26 ml) was stirred at 80-90 °C for 2 hours. The reaction mixture was poured into ice-water (100 ml) and extracted 3 times with ethyl acetate (40 ml). The extract was washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (100 g) eluting with a mixture of n-hexane and ethyl acetate (3:1 v/v). The fractions containing the desired compound were collected and evaporated in vacuo to give (2S,4R)-2[(3-azido-2-hydroxypropyl)thiomethyl]-4-t-butyldimethylsilyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.95 g).

IR (Neat) : 2110, 1740, 1710-1700, 1680-1665, 1610, 1525, 1350, 1255 cm^{-1}

Preparation 42

To a solution of (2S,4R)-2-[(3-azido-2-hydroxypropyl)thiomethyl]-4-t-butyldimethylsilyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.94 g) in pyridine (6 ml) was added triphenylphosphine (1.55 g) and the mixture was stirred at ambient temperature for 1 hour. To the reaction mixture was added conc. ammonia (0.50 ml) and the mixture was allowed to stand overnight at ambient temperature. The reaction mixture was concentrated under reduced pressure. The resulting mixture was dissolved in ethyl acetate (40 ml) and the solution was washed with saturated aqueous sodium chloride,dried over magnesium sulfate and evaporated in vacuo to give (2S,4R)-2-[(3-amino-2-hydroxypropyl)thiomethyl]-4-t-butyldimethylsilyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine. The residue containing the compound obtained above was dissolved in a mixture of ethyl acetate and water (3:1 V/V, 40 ml). To the solution was dropwise added a solution of 4-nitrobenzyloxycarbonyl chloride (0.87 g) in tetrahydrofuran (3 ml) with stirring at 2-5 °C, keeping the pH between 9-10 with 1N sodium hydroxide. The mixture was stirred at the same temperature for 1 hour. The organic layer was separated, washed with saturated aqueous sodium chloride, dried over magnesium sulfate and evaporated in vacuo. The resulting residue was chromatographed on silica gel (100 g) eluting with a mixture of dichloromethane and acetone (9:1 v/v). The fractions containing the desired compound were collected and evaporated in vacuo to give (2S,4R)-2-{3-(4-nitrobenzyloxycarbonyl)amino-2-hydroxypropyl}thiomethyl-4-t-butyldimethylsilyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (2.25 g).

IR (Neat) : 1710-1700, 1610, 1525, 1350, 1260 cm^{-1}

NMR ($CDCl_3$, δ) : 0.06 (6H, s), 0.86 (9H, s), 1.90-2.20 (2H, m), 5.15-5.30 (4H, m), 7.52 (4H, d, J=8Hz), 8.25 (4H, d, J=8Hz)

Preparation 43

To a solution of (2S,4R)-2-[3-(4-nitrobenzyloxycarbonyl)amino-2-hydroxypropyl]thiomethyl-4-t-butyldimethylsilyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (2.24 g) in dichloromethane (40 ml) were added pyridine (0.52 ml) and acetyl chloride (0.46 ml) under ice-cooling with stirring. The mixture was stirred at the same temperature for 1 hour. The reaction mixture was washed with water, saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride, in turn, dried over anhydrous magnesium sulfate, and evaporated in vacuo to give (2S,4R)-2-[2-acetoxy-3-(4-nitrobenzyloxycarbonyl)aminopropyl]-thiomethyl-4-t-butyldimethylsilyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (2.37 g).

NMR ($CDCl_3$, δ) : 0.06 (6H, s), 0.83 (9H, s), 2.06 (3H, d, J = 3Hz), 5.15-5.30 (4H, m), 8.22 (4H, d, J = 8Hz)

Preparation 44

(2S,4R)-2-[2-Acetoxy-3-(4-nitrobenzyloxycarbonyl)aminopropyl]thiomethyl-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.94 g) was obtained by reacting (2S,4R)-4-[2-acetoxy-3-(4-nitrobenzyloxycarbonyl)aminopropyl]thiomethyl-4-t-butyldimethylsilyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (2.36 g) with conc. hydrochloric acid (0.54 ml) in substantially the same manner as that of Preparation 9.

NMR ($CDCl_3$, δ) : 2.06 (3H, s), 5.15-5.35 (4H, m), 7.40-7.60 (4H, m), 8.21 (4H, d, J = 8Hz)

Preparation 45

(2S,4S)-2-[2-Acetoxy-3-(4-nitrobenzyloxycarbonyl)aminopropyl]thiomethyl-4-benzoylthio-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.51 g) was obtained by reacting (2S,4R)-2-[2-acetoxy-3-(4-nitrobenzyloxycarbonyl)aminopropyl]thiomethyl-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.94 g) with triphenylphosphine (1.10 g), and diethyl azodicarboxylate (0.66 ml) successively, and then with thiobenzoic S-acid (0.50 ml) in substantially the same manner as that of Preparation 4.

NMR ($CDCl_3$, δ) : 2.06 (3H, s), 4.90-5.20 (2H, m), 5.20-5.40 (4H, m), 7.40-7.70 (7H, m), 7.97 (2H, dd, J = 7Hz, J = 2Hz), 8.26 (4H, d, J = 8Hz)

Preparation 46

(2S,4S)-2-[2-Hydroxy-3-(4-nitrobenzyloxycarbonyl)aminopropyl]thiomethyl-4-mercapto-1-(4-nitrobenzyloxycarbonyl) pyrrolidine (0.49 g) was obtained by reacting (2S,4S)-2-[2-acetoxy-3-(4-nitrobenzyloxycarbonyl)aminopropyl]thiomethyl-4-benzoylthio-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.50 g) with 28% sodium methoxide-methanol solution (0.81 ml) in substantially the same manner as that of Preparation 7-1).

NMR ($CDCl_3$, δ) : 1.50-2.05 (3H, m), 2.40-3.60 (9H, m), 3.70-4.25 (3H, m), 5.22 (4H, s), 5.25-5.45 (1H, m) 7.53 (4H, d, J = 8Hz), 8.25 (4H, d, J = 8Hz)

Preparation 47

To a solution of (2S,4R)-2-aminomethyl-4-t-butyldimethylsilyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (2 g) were successively added triethylamine (0.82 ml) and methanesulfonyl chloride (0.42 ml) under ice-cooling with stirring, and the mixture was stirred at the same temperature for 1 hour. The reaction mexture was washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo to give (2S,4R)-2-methanesulfonylaminomethyl-4-t-butyldimethylsilyloxy- 1-(4-nitrobenzyloxycarbonyl)pyrrolidine (2.15 g).

IR (Neat) : 1705, 1690, 1610, 1530, 1350 cm^{-1}

NMR ($CDCl_3$, δ) : 0.08 (6H, s), 0.86 (9H, s), 1.80-2.20 (2H, m), 2.94 (3H, s), 4.00-4.55 (2H, m), 5.23-5.46 (2H, m), 7.55 (2H, m), 8.26 (1H, d, J = 9Hz)

Preparation 48

(2S,4R)-4-Hydroxy-2-methanesulfonylaminomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.57 g) was obtained by reacting (2S,4R)-4-t-butyldimethylsilyloxy-2-methanesulfonylaminomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (2.14 g) with conc. hydrochloric acid (0.73 ml) in substantially the same manner as that of Preparation 9.

IR (Neat) : 1760-1750, 1710-1690, 1640, 1605, 1515 cm^{-1}

Preparation 49

(2S,4R)-2-Methanesulfonylaminomethyl-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.63 g) was obtained by reacting (2S,4R)-4-hydroxy-2-methanesulfonylaminomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.62 g) with methanesulfonyl chloride (0.37 ml) in subatantially the same manner as that of Preparation 25-1).

NMR ($CDCl_3$, δ) : 2.00-2.70 (2H, m), 2.92 (3H, s), 3.03 (3H, s), 5.25 (2H, s), 7.55 (2H, d, J = 8Hz), 8.25 (2H, d, J = 8Hz)

EI MS : 277 (M^+ -174)

Preparation 50

To a suspension of sodium borohydride (0.5 g) in tetrahydrofuran (30 ml) was dropwise added boron trifluoride etherate (5.8 ml) under ice-cooling. After 30 minutes, a solution of (2S,4R)-2-(carbamoylmethyloxymethyl)-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (2.40 g) in tetrahydrofuran (10 ml) was added to the mixture under ice-cooling, and the mixture was stirred under the same condition for 2 hours and at ambient temperature for 18 hours. The mixture was concentrated under reduced pressure to give a residue. The residue was stirred in a mixture of concentrated hydrochloric acid (4 ml) and methanol (40 ml) at ambient temperature for 16 hours, and evaporated under reduced pressure to give a syrup. To a solution of the syrup in tetrahydrofuran (30 ml) were added triethylamine (1.2 ml) and methanesulfonyl chloride (0.5 ml) in turn under ice-cooling. After stirring for 1 hour, the reaction mixture was poured into a mixture of ethyl acetate (150 ml) and water (100 ml). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to give a syrup. The syrup was subjected to a column chromatography on silica gel (30 g) and eluted with a mixture of methanol and chloroform (3:97 V/V) to give (2S,4R)-2-[2-(methanesulfonylamino)ethyloxymethyl]-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.30 g).

IR (Neat) : 1705-1685, 1605 cm^{-1}

NMR ($CDCl_3$, δ) : 2.96 (3H, s), 3.03 (3H, s), 5.23 (2H, s), 7.48 (2H, d, J = 8.5Hz), 8.18 (2H, d, J = 8.5 Hz).

Preparation 51-1)

(2S,4S)-4-Acetylthio-2-methanesulfonylaminomethyl-1-(4-nitrobezyloxycarbonyl)pyrrolidine (1.16 g) was obtained by reacting (2S,4R)-2-methanesulfonylaminomethyl-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.61 g) with potassium thioacetate (0.81 g) in substantially the same manner as that of Preparation 30-1).

NMR ($CDCl_3$, δ) : 1.50-2.20 (2H,m), 2.33 (3H, s), 2.92 (3H, s), 3.10-3.60 (3H, m), 3.70-4.25 (3H, m), 5.23 (2H, s), 7.55 (2H, d, J = 9Hz) 8.22 (2H, d, J = 9Hz)

Preparation 51-2)

(2S,4S)-4-Acetylthio-2-[2-(methanesulfonylamino)ethyloxymethyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (0.80 g) was obtained by reacting (2S,4R)-2-[2-(methanesulfonylamino)ethyloxymethyl]-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.28 g) with thioacetic S-acid in substantially the same manner as that of Preparation 30-1).

IR (Neat) : 1705-1685, 1605 cm^{-1}

NMR ($CDCl_3$, δ) : 2.33 (3H, s), 2.96 (3H, s), 5.20 (2H, s), 7.48 (2H, d, J = 8.5Hz), 8.18 (2H, d, J = 8.5Hz)

Preparation 52-1)

(2S,4S)-4-Mercapto-2-methanesulfonylaminomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (0.72 g) was obtained by reacting (2S,4S)-4-acetylthio-2-methanesulfonylaminomethyl-1-(4-nitrobenzyloxycarbonyl)-pyrrolidine (1.15 g) with 28% sodium methoxide-methanol solution (0.61 ml) in substantially the same manner as that of Preparation 31-1).

NMR ($CDCl_3$, δ) : 1.50-2.05 (2H, m), 2.40-2.80 (1H, m), 2.95 (3H, s), 3.00-3.75 (4H, m), 3.80-4.25 (2H, m) 5.25 (2H, s), 7.56 (2H, d, J = 9Hz), 8.30 (2H, d, J = 9Hz)

Preparation 52-2)

(2S,4S)-4-Mercapto-2-[2-(methanesulfonylamino)ethyloxymethyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (0.53 g) was obtained by reacting (2S,4S)-4-acetylthio-2-[2-(methanesulfonylamino)ethyloxymethyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidin (0.79 g) with 28% sodium methoxide-methanol solution in substantially the sam manner as that of Preparation 31-1).

IR (Neat) : 1705-1685, 1605 cm^{-1}

NMR ($CDCl_3$, δ) : 2.96 (3H, s), 5.21 (2H, s), 7.48 (2H, d, J = 8.5Hz), 8.20 (2H, d, J = 8.5Hz)

Preparation 53

To a mixture of dimethylformamide (1.50 ml) and tetrahydrofuran (10 ml) was dropwise added phosphorus oxychloride (1.50 ml) at -5 ~ 5 °C and the mixture was stirred at the same temperature for 30 minutes. To the mixture was added a solution of (2S,4R)-2-carboxymethyloxymethyl-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (2.30 g) in tetrahydrofuran (20 ml) at -5 ~ 5 °C, followed by stirring at the same temperature for 30 minutes. The mixture was dropwise added to concentrated ammonia water (30 ml) at 0 - 10 °C with stirring. The mixture was stirred at the same condition for 2 hours. Tetrahydrofuran was evaporated under reduced pressure to give a mixture. The mixture was extracted with ethyl acetate (50 ml x 3). The ethyl acetate layer was dried over magnesium sulfate and concentrated under reduced pressure to give a syrup. The syrup was subjected to a column chromatography on silica gel (20 g) and eluted with a mixture of methanol and chloroform (3:97 V/V) to give (2S,4R)-2-(carbamoylmethyloxymethyl)-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.43 g).

mp : 131-133 °C

IR (Nujol) : 1705-1685 cm^{-1}

NMR (DMSO-d_6, δ) : 1.8-2.1 (2H, m), 3.27 (2H, s), 3.2-3.45 (2H, m), 3.45-3.65 (2H, m), 3.77 (2H, s), 3.85-4.35 (2H, m), 4.90 (2H, d, J = 3Hz), 5.19 (2H, s), 7.08 (2H, br d, J = 15Hz), 7.57 (2H, d, J = 8.5Hz), 8.18 (2H, d, J = 8.5Hz)

EI MS : 295 (M^+-58), 278 (M^+-75), 265 (M^+-88)

Preparation 54

To a suspension of sodium borohydride (0.30 g) in tetrahydrofuran (15 ml) was added boron trifluoride etherate (3.5 ml) in a nitrogen stream with stirring at 0 - 10 °C. The mixture was stirred at the same temperature for 30 minutes. To the mixture was added a solution of (2S,4R)-2-(carbamoylmethyloxymethyl)-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.40 g) in tetrahydrofuran (3 ml) at 0 - 10 °C. The mixture was stirred at 0 - 10 °C for 3 hours and at ambient temperature overnight. Methanol (10 ml) was added to the reaction mixture at 0 - 10 °C. After 2 hours, insoluble material was filtered off and the filtrate was concentrated under reduced pressure to give a residue. A solution of the residue in a mixture of concentrated hydrochloric acid (3 ml) and methanol (30 ml) was stirred at ambient temperature for 20 hours. The mixture was concentrated under reduced pressure to give a syrup. A solution of the syrup in ethyl acetate (30 ml) was extracted with 1N hydrochloric acid (30 ml x 3). The aqueous solution was adjusted to pH 10 with aqueous sodium hydroxide and extracted with chloroform (30 ml x 3). The organic solution was dried over magnesium sulfate and concentrated under reduced pressure to give a syrup. The syrup was subjected to a column chromatography on silica gel (20 g) and eluted with a mixture of methanol and chloroform (5:95 and then 10:90 V/V) to give (2S,4R)-2-(2-aminoethyloxymethyl)-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.13 g).

IR (Neat) : 3500-3050, 1705 cm^{-1}

NMR ($CDCl_3$, δ) : 5.21 (2H, s), 7.48 (2H, d, J = 8.5Hz), 8.18 (2H, d, J = 8.5Hz)

Preparation 55

To a solution of (2S,4R)-2-(2-aminoethyloxymethyl)-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.12 g) in a mixture of water (20 ml) and tetrahydrofuran (40 ml) was added a solution of 4-nitrobenzyloxycarbonyl chloride (0.85 g) in tetrahydrofuran (4 ml) under ice-cooling with stirring, keeping the pH between 8.5-9.5 with 4N aqueous sodium hydroxide. The mixture was stirred at the same condition for 2 hours. The reaction mixture was evaporated under reduced pressure and then ethyl acetate (50 ml) was added thereto. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to give a syrup. The syrup was subjected to a column chromatography on silica gel (20 g) and eluted with a mixture

of methanol and chloroform (2:98 V/V) to give (2S,4R)-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)-2-[2-(4-nitrobenzyloxycarbonylamino)ethyloxymethyl]pyrrolidine (0.88 g).

IR (Nujol) : 1710-1685 cm^{-1}

Preparation 56

To a solution of (2S,4R)-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)-2-[2-(4-nitrobenzyloxycarbonylamino)-ethyloxymethyl]pyrrolidine (0.87 g) and triethylamine (0.35 ml) in a mixture of tetrahydrofuran (5 ml) and dichloromethane (10 ml) was dropwise added a solution of methanesulfonyl chloride (0.16 ml) in dichloromethane (2 ml) with stirring at 0 - 5 °C and the mixture was stirred at 0 - 5 °C for 30 minutes. The reaction mixture was washed with water (20 ml), dried over magnesium sulfate and concentrated under reduced pressure to give a syrup. The syrup was subjected to a column chromatography on silica gel (20 g) and eluted with a mixture of methanol and chloroform (1:99 V/V) to give (2S,4R)-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)-2-[2-(4-nitrobenzyloxycarbonylamino)ethyloxymethyl]pyrrolidine (0.92 g).

IR (Neat) : 1725-1700 cm^{-1}

NMR ($CDCl_3$, δ) : 2.2-2.6 (2H, m), 3.02 (3H, s), 3.2-4.3 (9H, m), 4.9-5.4 (6H, m), 7.45 (4H, d, J = 8.5Hz), 8.16 (4H, d, J = 8.5Hz)

Preparation 57-1)

(2S,4R)-4-Methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)-2-[2-(4-nitrobenzyloxycarbonylamino)-ethyloxymethyl]pyrrolidine (1.80 g) was obtained by reacting (2S,4R)-2-(carbamoylmethyloxymethyl)-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl(pyrrolidine (3.60 g) with a mixture of sodium borohydride (0.75 g) and boron trifluoride etherate (8.7 ml), concentrated hydrochloric acid (6 ml), and 4-nitrobenzyloxycarbonyl chloride (2.1 g) successively in substantially the same manners as that of Preparation 10 .

IR (Neat) : 1725-1700 cm^{-1}

NMR ($CDCl_3$, δ) : 2.2-2.6 (2H, m), 3.02 (3H, s), 3.2-4.3 (9H, m), 4.9-5.4 (6H, m), 7.45 (4H, d, J = 8.5Hz), 8.16 (4H, d, J = 8.5Hz)

Preparation 57-2)

(2S,4R)-2-[{1,1-Dimethyl-2-(4-nitrobenzyloxycarbonylamino)ethyl}oxymethyl]-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.78 g) was obtained by reacting (2S,4R)-2-(1-carbamoyl-1-methylethyl)oxymethyl-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.60 g) with a mixture of sodium borohydride (0.34 g) and boron trifluoride etherate (3.25 ml) and then with 4-nitrobenzyloxycarbonyl chloride (0.75 g) in substantially the same manners as those of Preparations 7 and 8.

IR (Neat) : 1725-1700, 1605 cm^{-1}

NMR ($CDCl_3$, δ) : 1.12 (6H, s), 3.06 (3H, s), 5.20 (2H, s), 5.23 (2H, s)

Preparation 58-1)

A solution of (2S,4R)-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)-2-[2-(4-nitrobenzyloxycarbonylamino)ethyloxymethyl]pyrrolidine (0.90 g) in dimethylformamide (2 ml) was added to a reaction mixture of thioacetic S-acid (0.16 ml) and sodium hydride (62.8% in oil suspension) (0.07 g) in dimethylformamide (9 ml) in a nitrogen stream and the mixture was heated at 70 - 75 °C for 6 hours. The mixture was poured into water (100 ml), extracted with ethyl acetate (50 ml x 2), dried over magnesium sulfate and concentrated under reduced pressure to give a syrup. The syrup was subjected to a column chromatography on silica gel (20 g) and eluted with chloroform to give (2S,4S)-4-acetylthio-1-(4-nitrobenzyloxycarbonyl)-2-[2-(4-nitrobenzyloxycarbonylamino)ethyloxymethyl]pyrrolidine (0.60 g).

IR (Neat) : 1725-1685 cm^{-1}

NMR ($CDCl_3$, δ) : 2.30 (3H, s)

Preparation 58-2)

Crude product of (2S,4S)-4-acetylthio-2-[{1,1-dimethyl-2-(4-nitrobenzyloxycarbonylamino)-ethyl}oxymethyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.77 g) was obtained by reacting (2S,4R)-2-[{1,1-dimethyl-2-(4-nitrobenzyloxycarbonylamino)ethyl}oxymethyl]-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.77 g) with thioacetic S-acid in substantially the same manner as that of

Preparation 58-1).

IR (Neat) : 1720-1690, 1605 cm^{-1}

NMR ($CDCl_3$, δ) : 1.13 (6H, s), 2.31 (3H, s)

Preparation 59-1)

To a solution of (2S,4S)-4-acetylthio-1-(4-nitrobenzyloxycarbonyl)-2-[2-(4-nitrobenzyloxycarbonylamino)-ethyloxymethyl]pyrrolidine (0.59 g) in a mixture of methanol (12 ml) and tetrahydrofuran (12 ml) was added sodium methoxide (28% solution in methanol) (0.25 ml) at -20 ∼ -10 °C in a nitrogen stream and the mixture was stirred at the same condition for 1 hour. To the mixture was added glacial acetic acid (0.1 ml) at -10 ∼ 0 °C. The mixture was concentrated under reduced pressure to give a residue. The residue was dissolved in ethyl acetate (20 ml). The solution was washed with water (20 ml), dried over magnesium sulfate and concentrated under reduced pressure to give a syrup. The syrup was subjected to a column chromatography on a silica gel (10 g) and eluted with a mixture of acetone and chloroform (5:95 V/V) to give (2S,4S)-4-mercapto-1-(4-nitrobenzyloxycarbonyl)-2-[2-(4-nitrobenzyloxycarbonylamino)ethyloxymethyl]-pyrrolidine (0.46 g).

IR (Neat) : 1725-1690 cm^{-1}

Preparation 59-2)

(2S,4S)-2-[{1,1-Dimethyl-2-(4-nitrobenzyloxycarbonylamino)ethyl}oxymethyl]-4-mercapto-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (0.71 g) was obtained by reacting (2S,4S)-4-acetylthio-2-[{1,1-dimethyl-2-(4-nitrobenzyloxycarbonylamino)ethyl}oxymethyl]-1-(4-nitrobenzyloxy carbonyl)pyrrolidine (2.00 g) with 28% sodium methoxide-methanol solution (0.75 ml) in substantially the same manner as that of Preparation 59-1).

IR (Neat) : 1725-1680, 1605 cm^{-1}

NMR ($CDCl_3$, δ) : 1.13 (6H, s)

Preparation 60

To a solution of (2S, 4R)-2-aminomethyl-4-t-butyldimethylsilyloxy-1-(4-nitrobenzyloxycarbonyl)-pyrrolidine (8.43 g) in dichloromethane (80 ml) were added t-butoxycarbonylglycine (3.61 g), 1-hydroxybenzotriazole (2.78 g) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (3.95 g) under ice-cooling. The mixture was stirred under ice-cooling for 1 hour and at ambient temperature for 15 hours. The solution was washed with water (80 ml), saturated aqueous sodium hydrogen carbonate (80 ml), and brine (80 ml) successively, dried over magnesium sulfate, and concentrated under reduced pressure to give a syrup. The syrup was subjected to a column chromatography on silica gel (80 g) and eluted with a mixture of methanol and chloroform (2:98 v/v) to give (2S, 4R)-4-t-butyldimethylsilyloxy-2-[(t-butoxycarbonylamino)-methylcarbonyl]aminomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (9.07 g).

IR ($CHCl_3$) : 3330, 1720-1660 cm^{-1}

NMR ($CDCl_3$, δ) : 0.03 (6H, s), 0.85 (9H, s), 1.58 (9H, s), 7.52 (2H, d, J = 7.5Hz), 8.92 (2H, d, J = 7.5Hz)

Preparation 61

To a solution of (2S, 4R)-4-t-butyldimethylsilyloxy-2-[(t-butoxycarbonylamino)methylcarbonyl]-aminomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (9.05 g) in tetrahydrofuran (90 ml) was added a 1M solution (31.9 ml) of tetrabutylammonium fluoride in tetrahydrofuran at 0∼10 °C. The mixture was stirred at 0∼10 °C for 1 hour and at ambient temperature for 3 hours. The mixture was poured into a mixture of water (100 ml) and ethyl acetate (200 ml). The organic layer was separated, dried over magnesium sulfate and concentrated under reduced pressure to give a syrup. The syrup was subjected to a column chromatography on silica gel (80 g) and eluted with a mixture of methanol and dichloromethane (3:97 v/v) to give (2S,4R)-2-[(t-butoxycarbonylamino)methylcarbonyl]amino-methyl-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)-pyrrolidine (5.32 g).

IR ($CHCl_3$) : 3400-3200, 1710-1740 cm^{-1}

NMR ($CDCl_3$, δ) : 1.43 (9H, s)

Preparation 62

A solution of (2S, 4R)-2-[(t-butoxycarbonylamino)methylcarbonyl]aminomethyl-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidin (5.30 g) in a mixture of anisole (1 ml) and trifluoroacetic acid (50 ml) was stirred at ambient temperature for 1 hour. The mixture was evaporated under reduced pressure to give (2S, 4R)-2-(aminomethylcarbonyl)aminomethyl-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine. To a solution of the compound obtained above in a mixture of water (25 ml) and tetrahydrofuran (25 ml) was added a solution of potassium cyanate (4.75 g) in water (15 ml) at 40~50 °C, keeping the pH between 4-5 with concentrated hydrochloric acid. Tetrahydrofuran was removed by evaporation to give an aqueous solution. The aqueous solution was adjusted to pH 6.0 with 1N hydrochloric acid, subjected to a column chromatography on nonionic adsorption resin, "Diaion HP-20" (50 ml), washed with water, and eluted with a mixture of methanol and water (50:50 v/v). The fractions containing the desired compound were collected, concentrated under reduced pressure, and recrystallized from a mixture of methanol and diisopropyl ether to give (2S, 4R)-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)-2-[(ureidomethylcarbonyl)aminomethyl]pyrrolidine (3.93 g).

mp : 167-169 °C

IR (Nujol) : 3500-3200, 1685, 1660, 1640 cm^{-1}

MS: 395 (M^+), 369 (M^+-26), 300

Preparation 63

To a suspension of sodium borohydride (1.38 g) in tetrahydrofuran (50 ml) was added boron trifluoride etherate (4.49 ml) in a nitrogen stream with stirring at 0~5 °C. The mixture was stirred at the same condition for 30 minutes. To the mixture was added a solution of (2S, 4R)-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)-2-[(ureidomethylcarbonyl)aminomethyl]pyrrolidine (2.90 g) at 0~5 °C. The mixture was stirred at 0~5 °C for 1 hour and at ambient temperature overnight. Ethanol (30 ml) was added to the reaction mixture at 0~10 °C. After stirring for 2 hours, insoluble material was filtered off and the filtrate was concentrated under reduced pressure to give a residue. A solution of the residue in a mixture of concentrated hydrochloric acid (2.9 ml) and methanol (29 ml) was stirred at ambient temperature for 20 hours. The mixture was concentrated under reduced pressure to give (2S, 4R)-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)-2-[(2-ureidoethyl)aminomethyl]-pyrrolidine hydrochloride. To a solution of the compound obtained above in a mixture of water (20 ml) and tetrahydrofuran (20 ml) was added a solution of 4-nitrobenzyloxycarbonyl chloride (1.60 g) in tetrahydrofuran (5 ml) under ice-cooling, keeping the pH between 8.5-9.5 with concentrated hydrochloric acid. The reaction mixture was extracted with ehtyl acetate (100 ml). The organic layer was washed with brine (50 ml X 2), dried over magnesium sulfate, and concentrated under reduced pressure to give a syrup. The syrup was subjected to a column chromatography on silica gel (20 g) and eluted with a mixture of methanol and chloroform (5:95 v/v) to give (2S, 4R)-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)-2-[N-(4-nitrobenzyloxycarbonyl)-N-(2-ureidoethyl)amino]methylpyrrolidine (1.78 g).

IR ($CHCl_3$) : 3500-3200, 1705-1650 cm^{-1}

Preparation 64

To a solution of (2S, 4R)-4-hydroxy-1-(4-nitrobenzyloxycarbonyl)-2-[N-(4-nitrobenzyloxycarbonyl)-N-(2-ureidoethyl)amino]methylpyrrolidine (1.75 g) in pyridine (17.5 ml) was added methanesulfonyl chloride (0.60 ml) at 0~10 °C. The mixture was stirred at the same temperature for 1 hour and at ambient temperature for 15 hours. The mixture was poured into a mixture of water (100 ml) and ethyl acetate (100 ml). The organic layer was washed in turn with 1N hydrochloric acid (100 ml x 3), saturated sodium hydrogen carbonate (100 ml) and brine (100 ml), dried over magnesium sulfate and concentrated under reduced pressure to give a syrup. The syrup was subjected to a column chromatography on silica gel (30 g) and eluted with a mixture of methanol and chloroform (1:99 v/v) to give (2S, 4R)-2-[N-{2-(cyanoamino)ethyl}-N-(4-nitrobenzyloxycarbonyl)aminomethyl]-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.53 g).

IR ($CHCl_3$) : 2240, 1715-1685 cm^{-1}

NMR ($CDCl_3$, δ) : 3.03 (3H, s), 5.20 (4H, s), 7.48 (4H, d, J = 7.5 Hz), 8.20 (4H, d, J = 7.5 Hz)

Preparation 65

To a solution of (2S, 4R)-2-[N-{2-(cyanoamino)ethyl}-N-(4-nitrobenzyloxycarbonyl)aminomethyl]-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.52 g) in acetone (30 ml) was added oxalic acid dihydrate (1.92 g) at ambient temperature. The mixture was stirred at the same temperature for 18

hours. Ac tone was removed by evaporation to give a residue. A suspension of the syrup in ethyl acetate (100 ml) was washed in turn with 1N aqueous sodium hydroxide (50 ml x 2), water (50 ml) and brine (50 ml), dried over magnesium sulfat and conc ntrated under reduced pressure to give a syrup. The syrup was subjected to a column chromatography on silica gel (20 g) and eluted with a mixture of methanol and chloroform (2:98 v/v) to give (2S, 4R)-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)-2-[N-(4-nitrobenzyloxycarbonyl)-N-(2-ureidoethyl)aminomethyl]pyrrolidine (1.43 g).

IR ($CHCl_3$) : 3500-3200, 1710-1670 cm^{-1}

NMR ($CDCl_3$, δ) : 3.03 (3H, s), 5.21 (4H, s), 7.52 (4H, d, J = 7.5 Hz), 8.22 (4H, d, J = 7.5 Hz).

Preparation 66

(2S, 4S)-4-Acetylthio-1-(4-nitrobenzyloxycarbonyl)-2-[N-(4-nitrobenzyloxycarbonyl)-N-(2-ureidoethyl)-aminomethyl]pyrrolidine (1.11 g) was obtained by reacting (2S, 4R)-4-methanesulfonyloxy-1-(4-nitrobenzyloxycarbonyl)-2-[N-(4-nitrobenzyloxycarbonyl)-N-(2-ureidoethyl)aminomethyl]pyrrolidine (1.40 g) with thioacetic S-acid (0.25 ml) in substantially the same manner as that of Preparation 58-1).

IR ($CHCl_3$) : 3500-3200, 1710-1655 cm^{-1}

NMR ($CDCl_3$, δ) : 2.32 (3H, s), 5.20 (4H, s), 7.52 (4H, d, J = 7.5 Hz), 8.25 (4H, d, J = 7.5 Hz).

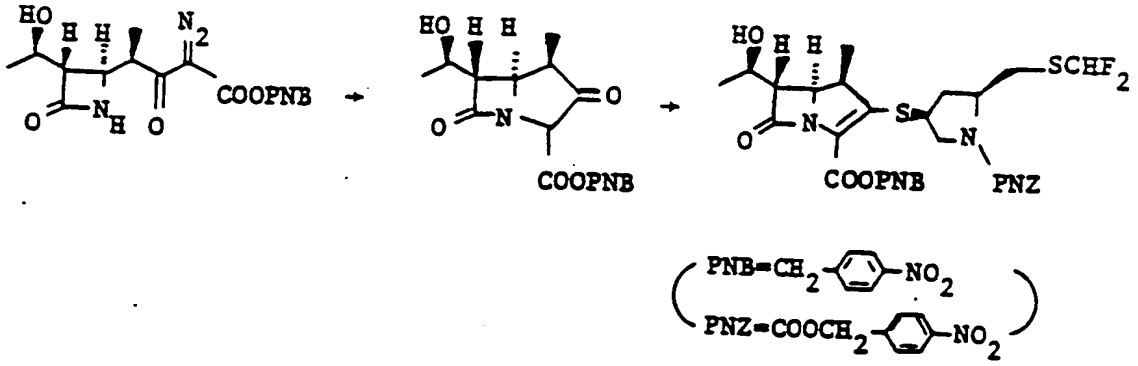
Preparation 67

(2S, 4S)-4-Mercapto-1-(4-nitrobenzyloxycarbonyl)-2-[N-(4-nitrobenzyloxycarbonyl)-N-(2-ureidoethyl)-aminomethyl]pyrrolidine (0.77 g) was obtained by reacting (2S, 4S)-4-acetylthio-1-(4-nitrobenzyloxycarbonyl)-2-[N-(4-nitrobenzyloxycarbonyl)-N-(2-ureidoethyl)aminomethyl]pyrrolidine (1.06 g) with 28% solution (0.45 ml) of sodium methoxide in methanol in substantially the same manner as that of Preparation 59-1).

IR ($CHCl_3$) : 3500-3200, 1715-1655 cm^{-1}

NMR ($CDCl_3$, δ) : 7.54 (4H, d, J = 7.5 Hz), 8.25 (4H, d, J = 7.5 Hz)

Example 1



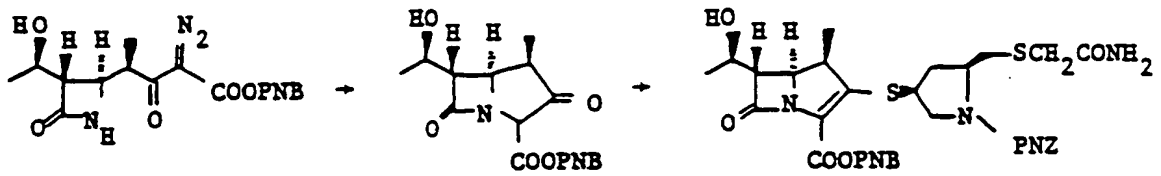
To a solution of 4-nitrobenzyl (4R)-2-diazo-4-[(2R, 3S)-3-{(1R)-1-hydroxyethyl}-4-oxoazetidin-2-yl]-3-oxopentanoate (0.5 g) in 1,2-dichloroethane (10 ml) was added rhodium(II) acetate (2 mg) under refluxing. After refluxing for 30 minutes, the reaction mixture was cooled and evaporated in vacuo to give a residue. The residue was dissolved in anhydrous benzene (10 ml) and then evaporated. This operation was repeated once again and the residue was dried in vacuo to give 4-nitrobenzyl (4R,5R,6S)-6-[(1R)-1-hydroxyethyl]-4-methyl-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate. The compound obtained above was dissolved in anhydrous acetonitrile (10 ml) and cooled to 0 °C under an atmosphere of nitrogen. To this solution were added N,N-diisopropyl-N-ethylamine (0.27 ml) and diphenyl phosphorochloridate (0.28 ml) successively, and the solution was stirred at 0 °C for 40 minutes. To th resulting solution were added dropwis a solution of (2S,4S)-2-(difluoromethyl)thiomethyl-4-mercapto-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (0.54 g) in anhydrous acetonitrile (3 ml) and N,N-diisopropyl-N-ethylamine (0.29 ml) at 5 °C with stirring, and th stirring

was continued at the same temperature for 2 hours. To the reaction mixture was added ethyl acetate (30 ml). Th solution was washed twice with saturated aqueous sodium chloride (20 ml), dried over anhydrous magnesium sulfate and evaporated. The oily residue was chromatographed on silica gel (60 g) eluting with a mixture of dichloromethane and acetone (5:1,V/V) to give 4-nitrobenzyl(4R,5S,6S)-3-[(2S,4S)-2-(difluoromethyl)thiomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (0.58 g).

IR (Nujol) : 1770, 1760, 1710, 1690, 1610, 1525, 1350 cm^{-1}

NMR ($CDCl_3$, δ) : 1.30 (3H, d, J = 7Hz), 1.35 (3H, d, J = 7Hz), 1.70-2.10 (2H, m), 5.15-5.50 (4H, m), 6.80 (1H, t, J = 56Hz), 7.53 (2H, d, J = 8Hz), 7.65 (2H, d, J = 8Hz), 8.37 (4H, d, J = 8Hz)

Example 2

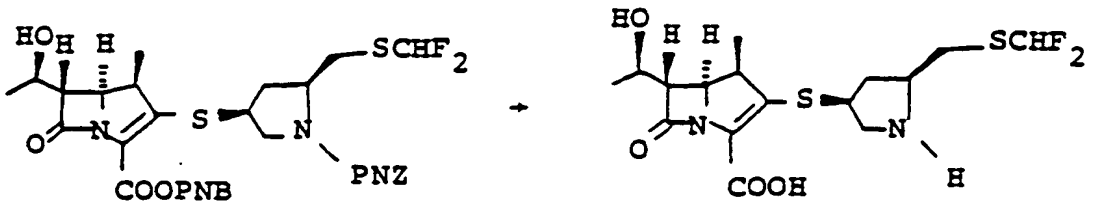


To a solution of 4-nitrobenzyl (4R)-2-diazo-4-[(2R,3S)-3-{(1R)-1-hydroxyethyl}-4-oxoazetidin-2-yl]-3-oxopentanoate (0.4 g) in 1,2-dichloroethane was added rhodium(II) acetate (1 mg) under refluxing. After refluxing for 1 hour, the reaction mixture was cooled and evaporated in vacuo to give a residue. The residue was dissolved in anhydrous benzene (10 ml) and then evaporated in vacuo. This operation was repeated once again and the residue was dried in vacuo to give 4-nitrobenzyl (4R,5R,6S)-6-[(1R)-1-hydroxyethyl]-4-methyl-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate. The compound obtained above was dissolved in anhydrous acetonitrile (10 ml) and cooled to 0 °C under an atmosphere of nitrogen. To this solution were added N,N-diisopropyl-N-ethylamine (0.21 ml) and diphenyl phosphorochloridate (0.22 ml) successively, and the solution was stirred at 0 °C for 40 minutes. To the resulting solution were added dropwise a solution of (2S,4S)-2-(carbamoylmethyl)thiomethyl-4-mercapto-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (0.45 g) in N,N-dimethylformamide (3 ml) and N,N-diisopropyl-N-ethylamine (0.21 ml) at 0-2 °C with stirring and the stirring was continued at the same temperature for 2 hours. To the reaction mixture was added ethyl acetate (30 ml). The solution was washed 3 times with saturated aqueous sodium chloride (20 ml), dried over anhydrous magnesium sulfate and evaporated in vacuo to give a residue. The residue was chromatographed on silica gel (60 g) eluting with a mixture of dichloromethane and acetone (1:1,V/V). The fractions containing the desired compound were collected and evaporated in vacuo to give 4-nitrobenzyl (4R,5S,6S)-3-[(2S,4S)-2-(carbamoylmethyl)thiomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate(0.44 g).

IR (Nujol) : 1760, 1710-1700, 1690-1670, 1610, 1540-1515 cm^{-1}

NMR ($CDCl_3$, δ): 1.26 (3H, d, J = 7Hz), 1.35 (3H, d, J = 7Hz), 1.55-2.10 (6H, m), 3.20 (2H, s), 3.20-3.50 (3H, m), 3.85-4.40 (4H, m), 5.10-5.70 (4H, m), 7.53 (2H, d, J = 7Hz), 7.65 (2H, d, J = 7Hz), 8.24 (4H, d, J = 7Hz)

Example 3



A mixture of 4-nitrobenzyl (4R,5S,6S)-3-[(2S,4S)-2-(difluoromethyl)thiomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (0.58 g), 20% palladium hydroxide on carbon (0.5 g), 0.05 M phosphate buffer (pH 6.3, 18 ml) and tetrahydrofuran (18 ml) was stirred at ambient temperature for 4 hours under atmospheric pressure of hydrogen. After the catalyst was filtered off, the filtrate was concentrated under reduced pressure to remove the organic solvent. The resulting aqueous residue was washed with ethyl acetate (10 ml x 2) and the aqueous layer was concentrated under reduced pressure to remove the organic solvent. The residue was chromatographed on nonionic adsorption resin "Diaion HP-20" (Trademark, made by Mitsubishi Chemical Industries) (20 ml) eluting in turn with water (80 ml) and 6% aqueous acetone (80 ml). The fractions containing the desired compound were collected and lyophilized to give (4R,5S,6S)-3-[(2S,4S)-2-(difluoromethyl)thiomethylpyrrolidin-4-ylthio]-6-[1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (0.19 g).

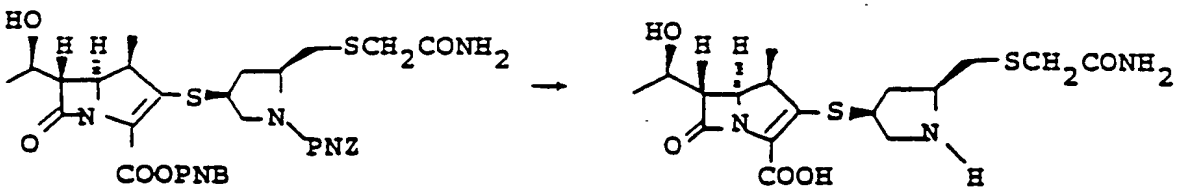
mp : >165 • C (dec.)

IR (Nujol) : 1760, 1590, 1180, 1150 cm^{-1}

NMR (D_2O, δ) : 1.22 (3H, d, J = 7Hz), 1.28 (3H, d, J = 7Hz), 1.71-1.86 (1H, m), 2.74-2.95 (1H, m), 3.20 (1H, dd, J = 10, 15Hz), 3.28-3.50 (3H, m), 3.69 (1H, dd, J = 8, 12Hz), 3.90-4.10 (2H, m), 4.18-4.30 (2H, m), 7.11 (1H, t, J = 55Hz)

SI Mass : 407 (M^+), 363 (M^+-44)

Example 4



A mixture of 4-nitrobenzyl (4R,5S,6S)-3-[(2S,4S)-2-(carbamoylmethyl)thiomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidin -4-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (0.42 g), 20% palladium hydroxide on carbon (0.4 g), 0.05 M phosphate buffer (pH 6.3, 20 ml), and tetrahydrofuran (20 ml) was stirred at ambient temperarure for 4 hours under atmospheric pressure of hydrogen. After the catalyst was filtered off, the filtrate was concentrated under reduced pressure to remove the organic solvent. The resulting residue was washed twice with ethyl acetate (20 ml) and the aqueous layer was concentrated under reduced pressure to remove the organic solvent. The residue was chromatographed on nonionic adsorption resin "Diaion HP-20" (Trademark, made by Mitsubishi Chemical Industries) (20 ml) eluting in turn with water (100 ml) and 5% aqueous acetone (100 ml). The fractions containing the desired compound were collected and lyophilized to give (4R,5S,6S)-3-[(2S,4S)-2-(carbamoylmethyl)-thiomethylpyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (0.16 g).

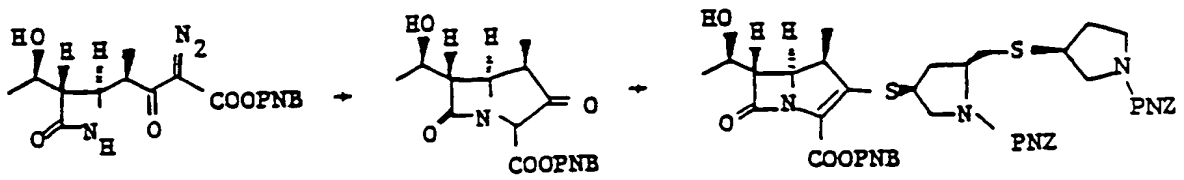
mp : 171-174 • C (dec.)

IR (Nujol) : 1750, 1670, 1580, 1150 cm^{-1}

NMR (D_2O, δ) : 1.21 (3H, d, J = 7Hz), 1.27 (3H, d, J = 7Hz), 1.45-2.00 (2H, m), 2.55-3.20 (5H, m), 3.39

(2H, s)

Example 5

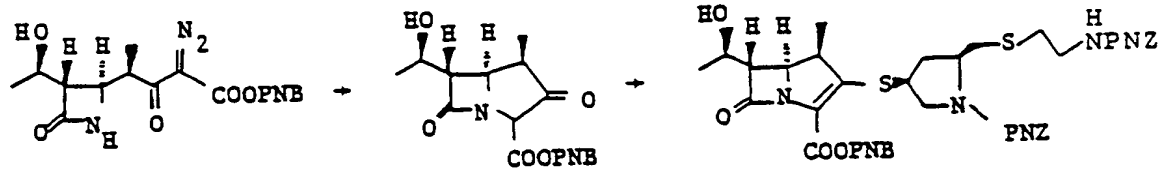


4-Nitrobenzyl (4R,5S,6S)-6-[(1R)-1-hydroxyethyl]-4-methyl-3-[(2S,4S)-1-(4-nitrobenzyloxycarbonyl)-2-[{-(3S)-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-3-ylthio}methyl]pyrrolidin-4-ylthio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (0.32 g) was obtained by reacting 4-nitrobenzyl (4R)-2-diazo-4-[(2R,3S)-3-{(1R)-1-hydroxyethyl}-4-oxoazetidin-2-yl]-3-oxopentanoate (0.30 g) with rhodium(II) acetate (1 mg), and then successively with diphenyl phosphorochloridate (0.17 ml) and (2S,4S)-4-mercapto-1-(4-nitrobenzyloxycarbonyl)-2-[{(3S)-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-3-ylthio}methyl]pyrrolidine (0.41 g) in substantially the same manner as that of Example 2.

IR (Neat) : 1775-1760, 1710, 1690, 1610, 1520 cm^{-1}

NMR ($CDCl_3$, δ) : 1.30 (3H, d, J = 7Hz), 1.38 (3H, d, J = 7Hz), 1.75-2.10 (3H, m), 2.80-3.90 (11H, m), 3.90-4.40 (4H, m), 5.20-5.50 (6H, m), 7.55 (4H, d, J = 8Hz), 7.66 (2H, d, J = 8Hz), 8.25 (6H, d, J = 8Hz)

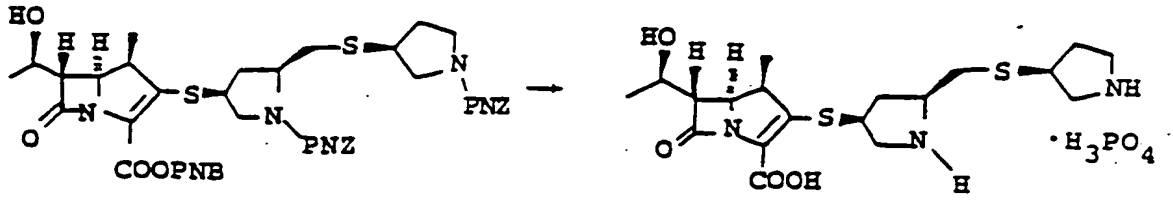
Example 6



4-Nitrobenzyl (4R,5S,6S)-6-[(1R)-1-hydroxyethyl]-4-methyl-3-[(2S,4S)-1-(4-nitrobenzyloxycarbonyl)-2-[{2-(4-nitrobenzyloxycarbonylamino)ethylthio}methyl]pyrrolidin-4-ylthio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (0.22 g) was obtained by reacting 4-nitrobenzyl (4R)-2-diazo-4-[(2R,3S)-3-{(1R)-1-hydroxyethyl}-4-oxoazetidin-2-yl]-3-oxopentanoate (0.30 g) with rhodium(II) acetate (1 mg), and then successively with diphenyl phosphorochloridate (0.17 ml) and (2S,4S)-4-mercapto-1-(4-nitrobenzyloxycarbonyl)-2-[{2-(4-nitrobenzyloxycarbonylamino)ethylthio}methyl]pyrrolidine (0.46 g) in substantially the same manner as that of Example 2.

IR (Neat) : 1765-1750, 1710, 1660-1640, 1530-1510 cm^{-1}

Example 7

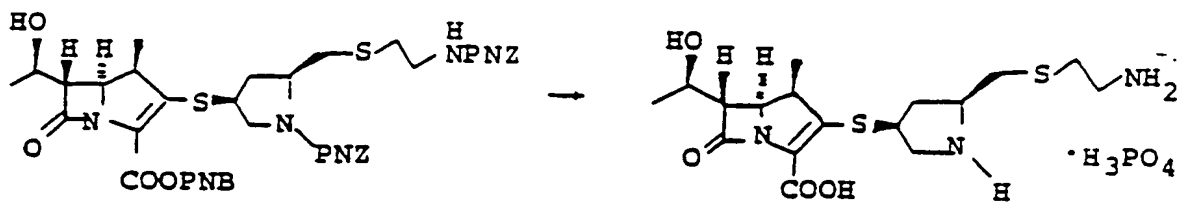


(4R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-4-methyl-7-oxo-3-[(2S,4S)-2-{(3S)-pyrrolidin-3-ylthiomethyl}pyrrolidin-4-ylthio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid phosphate (61.4 mg) was obtained by hydrogenating 4-nitrobenzyl (4R,5S,6S)-6-[(1R)-1-hydroxyethyl]-4-methyl-3-[(2S,4S)-1-(4-nitrobenzyloxycarbonyl)-2-[{(3S)-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-3-ylthio}methyl]pyrrolidin-4-ylthio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (350 mg) in substantially the same manner as that of Example 4.

IR (Nujol) : 1760-1740, 1580 cm^{-1}

NMR (D_2O, δ) : 1.22 (3H, d, J = 7Hz), 1.29 (3H, d, J = 7Hz), 1.46-1.95 (2H, m)

Example 8



(4R,5S,6S)-3-[(2S,4S)-2-{(2-Aminoethylthio)methyl}pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid phosphate (0.04 g) was obtained by hydrogenating 4-nitrobenzyl (4R,5S,6S)-6-[(1R)-1-hydroxyethyl]-4-methyl-3-[(2S,4S)-1-(4-nitrobenzyloxycarbonyl)-2-[{2-(4-nitrobenzyloxycarbonylamino)ethylthio}methyl]pyrrolidin-4-ylthio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (0.20 g) in substantially the same manner as that of Example 4.

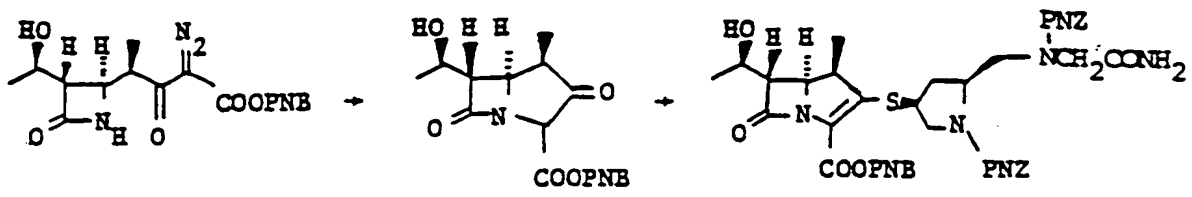
mp : >178 °C (dec.)

IR (Nujol) : 1750, 1590-1580 cm^{-1}

NMR (D_2O, δ) : 1.22 (3H, d, J = 7Hz), 1.30 (3H, d, J = 7Hz), 1.45-1.95 (2H, m), 2.55-3.08 (5H, m), 3.12-4.35 (9H, m)

SI Mass : 402 (M^+)

Example 9

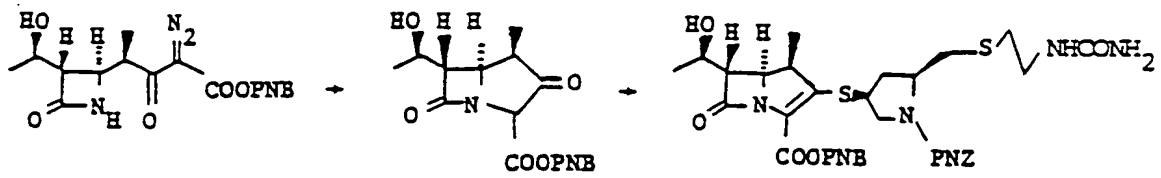


4-Nitrobenzyl (4R,5S,6S)-3-[(2S,4S)-2-{N-carbamoylmethyl-N-(4-nitrobenzyloxycarbonyl)}aminomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate (1.05 g) was obtained by reacting 4-nitrobenzyl (4R)-2-diazo-4-[(2R,3S)-3-{(1R)-1-hydroxyethyl}-4-oxoazetidin-2-yl]-3-oxopentanoate (0.85 g) with rhodium(II) acetate (1 mg), and then successively with diphenyl phosphorochloridate (0.47 ml) and (2S,4S)-2-[N-carbamoylmethyl-N-(4-nitrobenzyloxycarbonyl)]aminomethyl-4-mercapto-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (1.43 g) in substantially the same manner as that of Example 2.

IR (Nujol): 1755, 1710-1700, 1610, 1520, 1350 cm^{-1}

NMR ($CDCl_3$, δ): 1.24 (3H, d, J = 7Hz), 1.36 (3H, d, J = 7Hz), 3.15-3.46 (3H, m), 3.56-4.40 (12H, m), 5.12-5.50 (6H, m), 7.36-7.80 (6H, m), 8.24 (6H, d, J = 8Hz)

Example 10

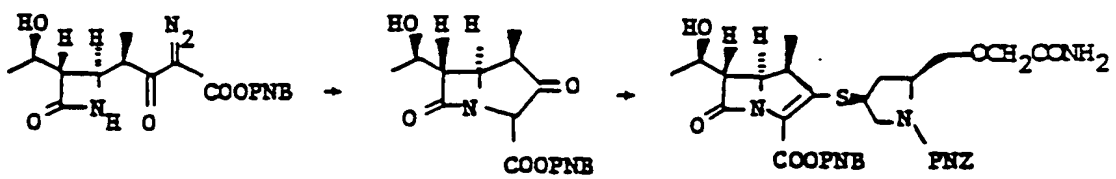


4-Nitrobenzyl (4R,5S,6S)-3-[(2S,4S)-2-(2-ureidoethyl)thiomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (0.97 g) was obtained by reacting 4-nitrobenzyl (4R)-2-diazo-4-[(2R,3S)-3-{(1R)-1-hydroxyethyl}-4-oxoazetidin-2-yl]-3-oxopentanoate (0.90 g) with rhodium(II) acetate (1 mg), and then successively with diphenyl phosphorochloridate (0.50 ml) and (2S,4S)-4-mercapto-2-(2-ureidoethyl)thiomethyl-1-(4-nitrobenzyloxycarbonyl)-pyrrolidine (1.05 g) in substantially the same manner as that of Example 2.

IR (Nujol): 1770, 1705, 1610, 1525, 1350 cm^{-1}

NMR ($CDCl_3$, δ): 1.25 (3H, d, J = 7Hz), 1.32 (3H, d, J = 6Hz), 3.10-4.38 (11H, m), 4.81 (2H, br s), 5.24 (2H, s), 5.38 (2H, dd, J = 14, 29Hz), 7.56 (2H, d, J = 8Hz), 7.68 (2H, d, J = 8Hz), 8.26 (4H, d, J = 8Hz)

Example 11



4-Nitrobenzyl (4R,5S,6S)-3-[(2S,4S)-2-(carbamoylmethyl)oxymethyl-1-(4-nitrobenzyloxycarbonyl)-pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (0.75

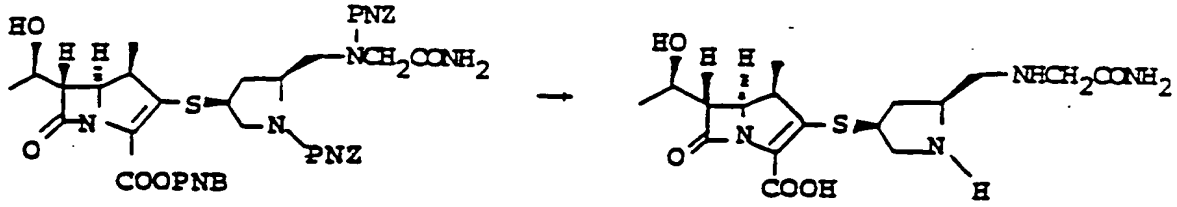
g) was obtained by reacting 4-nitrobenzyl (4R)-2-diazo-4-[(2R,3S)-3-{(1R)-1-hydroxyethyl}-4-oxoazetidin-2-yl]-3-oxopentanoate (0.62 g) with rhodium(II) acetate (2 mg), and then successively with diphenyl phosphorochloridate (0.35 ml) and (2S,4S)-2-(carbamoylmethyl)oxymethyl-4-mercapto-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (0.58 g) in substantially the same manner as that of Example 2.

mp: 58° - 64°C

IR (KBr): 1765, 1705-1675 cm^{-1}

NMR (D_2O, δ): 1.29 (3H, d, J=6Hz), 1.36 (3H, d, J=6.5Hz), 3.94 (2H, s), 7.45 (2H, d, J=8.5 Hz), 7.61 (2H, d, J=8.5Hz), 8.18 (4H, d, J=8.5Hz)

Example 12



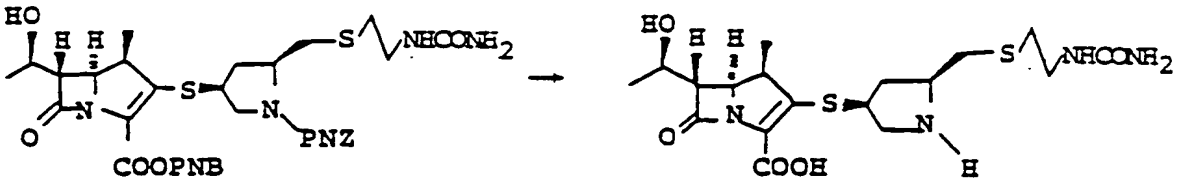
(4R,5S,6S)-3-[(2S,4S)-2-{(N-Carbamoylmethyl)aminomethyl}pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (0.30 g) was obtained by hydrogenating 4-nitrobenzyl (4R,5S,6S)-3-[(2S,4S)-2-{N-carbamoylmethyl-N-(4-nitrobenzyloxycarbonyl)}aminomethyl-1-(4-nitrobenzyloxycarbonyl) pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (1.03 g) in substantially the same manner as that of Example 4.

mp: >188°C (dec.)

IR (Nujol): 1760-1750, 1660-1640 cm^{-1}

NMR (D_2O, δ): 1.22 (3H, d, J=6Hz), 1.30 (3H, d, J=6Hz), 1.55-2.05 (2H, m), 2.50-2.96 (2H, m), 3.00-4.40 (10H, m)

Example 13



(4R,5S,6S)-3-[(2S,4S)-2-{(2-Ureidoethyl)thiomethyl}pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (0.30 g) was obtained by hydrogenating 4-nitrobenzyl (4R,5S,6S)-3-[(2S,4S)-2-(2-ureidoethyl)thiomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (0.95 g) in substantially the same manner as that of Example 4.

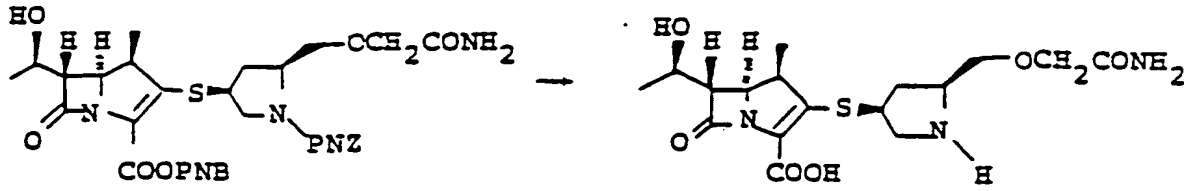
mp: >169°C (dec.)

IR (Nujol): 1755, 1650, 1580 cm^{-1}

NMR (D_2O, δ): 1.21 (3H, d, J=9Hz), 1.27 (3H, d, J=6Hz), 1.42-2.03 (2H, m), 2.53-4.36 (14H, m)

SI Mass: 445 (M^+), 444 (M^+-1), 443 (M^+-2)

Example 14



(4R,5S,6S)-3-[(2S,4S)-2-{(carbamoylmethyl)oxymethyl}pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicylco[3.2.0]hept-2-ene-2-carboxylic acid (0.33 g) was obtained by hydrogenating 4-nitrobenzyl (4R,5S,6S)-3-[(2S,4S)-2-(carbamoylmethyl)oxymethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (0.73 g) in substantially the same manner as that of Example 4.

mp: 165 °C (dec.)

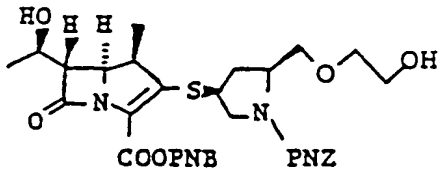
IR (KBr): 1745, 1670, 1585 cm^{-1}

NMR (D_2O, δ): 1.19 (3H, d, J = 6.5 Hz), 1.26 (3H, d, J = 6.5 Hz), 1.6-2.0 (1H, m), 2.5-2.9 (1H, m)

SI Mass: 400 ($M^+ + 1$)

The following compounds were obtained in substantially the same manner as that of Example 2.

Example 15

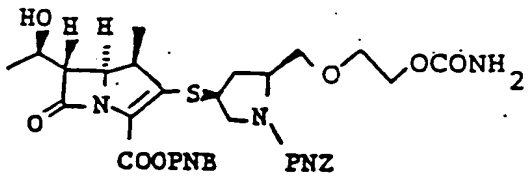


4-Nitrobenzyl (4R,5S,6S)-6-[(1R)-1-hydroxyethyl]-3-[2S,4S)-2-(2-hydroxyethyloxymethyl)-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-yl]thio-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

IR (Nujol): 3400, 1740-1770, 1680-1710, 1605 cm^{-1}

NMR ($CDCl_3$, δ): 1.1-1.6 (6H, m), 5.1-5.6 (4H, m), 7.3-7.7 (4H, m), 8.21 (4H, d, J = 9Hz)

Example 16

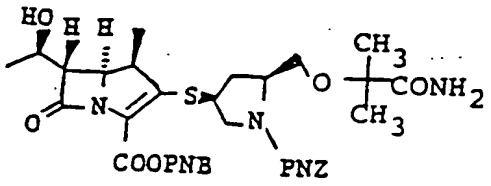


4-Nitrobenzyl (4R,5S,6S)-3-[(2S,4S)-2-(2-carbamoyloxyethyloxymethyl)-1-(4-nitrobenzyloxycarbonyl)-pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

IR (CH_2Cl_2): 3400-3500, 1765, 1700-1720, 1605 cm^{-1}

NMR ($CDCl_3$, δ): 1.1-1.7 (6H, m), 5.0-5.6 (4H, m), 7.4-7.8 (4H, m), 8.21 (4H, d, J = 8.5Hz)

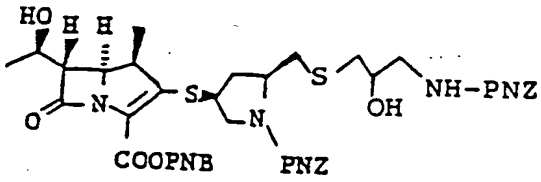
Example 17



4-Nitrobenzyl (4R,5S,6S)-3-[(2S,4S)-2-(1-carbamoyl-1-methylethyl)oxymethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

IR ($CHCl_3$) 1770, 1710-1680 cm^{-1}

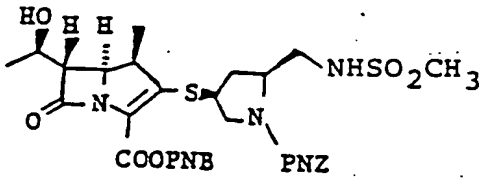
Example 18



4-Nitrobenzyl (4R,5S,6S)-3-[(2S,4S)-2-{2-hydroxy-3-(4-nitrobenzyloxycarbonylamino)propyl}thiomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate

NMR ($CDCl_3$, δ): 1.26 (3H, d, J = 9Hz), 1.36 (3H, d, J = 6Hz), 5.15-5.45 (6H, m), 7.40-7.75 (6H, m), 8.25 (6H, d, J = 8Hz)

Example 19



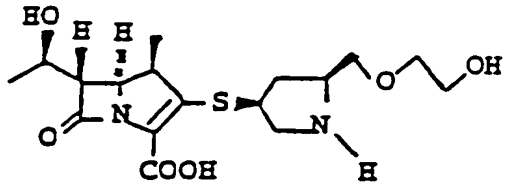
4-Nitrobenzyl (4R,5S,6S)-6-[(1R)-1-hydroxyethyl]-3-[(2S,4S)-2-(methylsulfonylamino)methyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-yl]thio-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

IR (Nujol): 1770-1750, 1710-1690, 1605, 1520 cm^{-1}

NMR ($CDCl_3$, δ): 1.28 (3H, d, J = 7Hz), 1.37 (3H, d, J = 7Hz), 1.65-2.10 (3H, m), 2.35-2.85 (2H, m), 2.94 (3H, s), 5.25 (4H, s), 5.40-5.75 (2H, m), 7.56 (2H, d, J = 9Hz), 7.66 (2H, d, J = 9Hz), 8.26 (4H, d, J = 9Hz)

The following compounds were obtained in substantially the same manner as that of Example 4.

Example 20



(4R,5S,6S)-6-[(1R)-1-hydroxyethyl]-3-[2S,4S)-2-(2-hydroxyethyloxymethyl)pyrrolidin-4-yl]thio-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

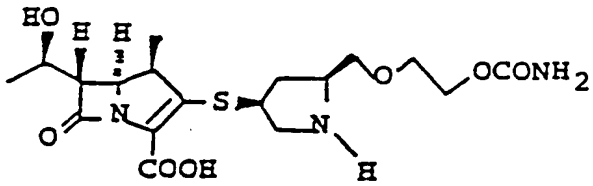
mp: 170-175 • C (dec.)

IR (KBr): 1730-1760, 1570-1590 cm^{-1}

NMR (D_2O, δ): 1.21 (3H, d, J = 8Hz), 1.28 (3H, d, J = 7Hz), 1.5-2.1 (1H, m), 2.4-2.9 (1H, m)

SIMS: 387 ($M^+ + 1$)

Example 21



(4R,5S,6S)-3-[(2S,4S)-2-(2-carbamoyloxyethyloxymethyl)pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-1-carboxylic acid

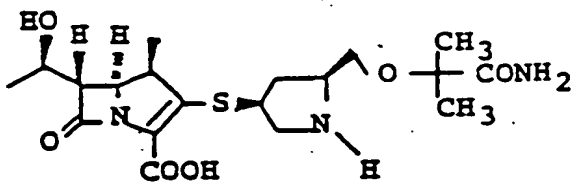
mp: 145-155 • C (dec.)

IR (KBr): 1750, 1705-1725, 1580 cm^{-1}

NMR (D_2O, δ): 1.22 (3H, d, J = 7Hz), 1.28 (3H, d, J = 6Hz), 1.6-1.9 (1H, m), 2.4-2.9 (1H, m)

SIMS: 430 ($M^+ + 1$)

Example 22



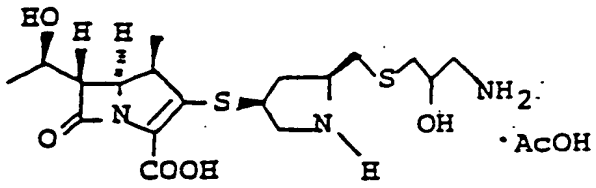
(4R,5S,6S)-3-[(2S,4S)-2-(1-carbamoyl-1-methylethyl)oxymethylpyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

mp: 175 • C (dec.)

IR (KBr): 1755-1730, 1670-1645 cm^{-1}

NMR (D_2O, δ): 1.18 (3H, d, J = 7Hz), 1.28 (3H, d, J = 7Hz), 1.44 (6H, s)

Example 23

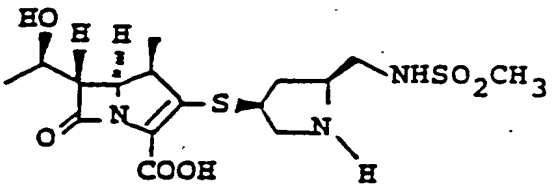


(4R,5S,6S)-3-[(2S,4S)-2-(3-amino-2-hydroxypropyl)thiomethylpyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid acetate

IR (Nujol): 1755-1740, 1585-1560 cm^{-1}

NMR (D_2O, δ): 1.22 (3H, d, J = 8Hz), 1.28 (3H, d, J = 6Hz), 1.55-2.00 (2H, m), 1.92 (3H, s)

Example 24



(4R,5S,6S)-6-[(1R)-1-hydroxyethyl]-3-[(2S,4S)-2-(methylsulfonylamino)methylpyrrolidin-4-yl]thio-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

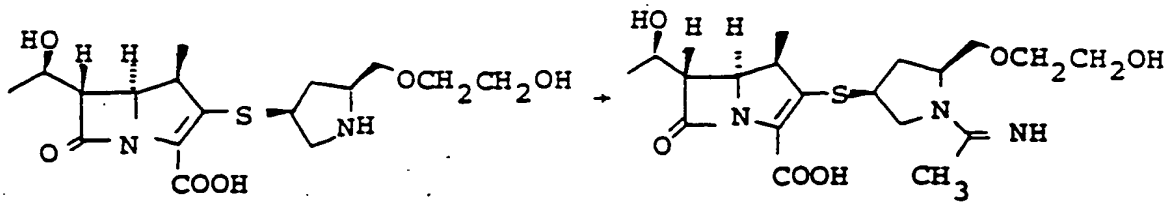
mp: >178 • C

IR (Nujol): 1760-1750, 1590-1580, 1150 cm^{-1}

NMR (D_2O, δ): 1.22 (3H, d, J = 7Hz), 1.28 (3H, d, J = 6Hz), 1.45-2.00 (2H, m), 2.46-2.95 (1H, m), 3.13 (3H, s)

SIMS: 420 (M^+)

Example 25



A solution of (4R,5S,6S)-6-[(1R)-1-hydroxyethyl]-3-[(2S,4S)-2-(2-hydroxyethyloxymethyl)pyrrolidin-4-ylthio]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (300 mg) in 0.05 M phosphate buffer (pH 7, 30 ml) was adjusted to pH 8.5 with 30% potassium carbonate at 0 • C, and ethyl acetimidate hydrochloride (3 g) was added in portions, while adjusting the mixture to around pH 8.5. After stirring for 1 hour, the reaction mixture was neutralized with 1N hydrochloric acid and washed with ethyl acetate and concentrated in vacuo. The residue was chromatographed on nonionic adsorption resin "Diaion HP-20" eluting successively with water and 5% aqueous acetone. The fractions containing the desired compound were collected and lyophilized to give (4R,5S,6S)-3-[(2S,4S)-1-acetimidoyl-2-(2-hydroxyethyloxymethyl)-

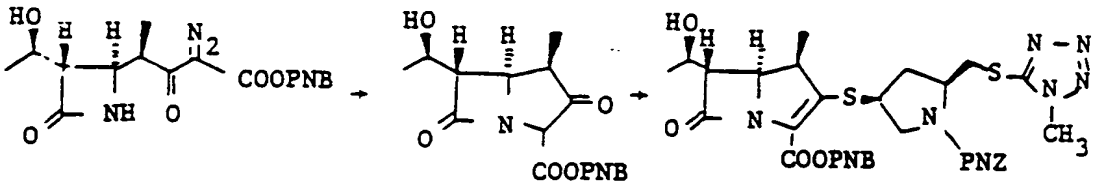
pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (290 mg).

IR (KBr) : 3100-3400, 1730-1750, 1580 cm^{-1}

NMR (D_2O, δ) : 1.19 (3H, d, J=7Hz), 1.28 (3H, d, J=6Hz), 2.28 (s) / 2.39 (s) (3H), 2.5-2.9 (1H, m)

SI Mass : 426 (M^+-1)

Example 26



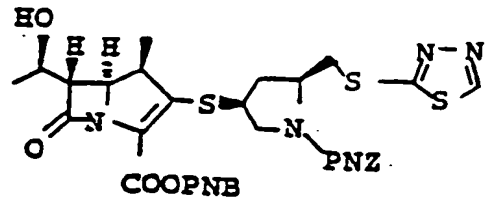
To a solution of 4-nitrobenzyl (4R)-2-diazo-4-[(2R,3S)-3-{(1R)-1-hydroxyethyl}-4-oxoazetidin-2-yl]-3-oxopentanoate (0.6 g) in anhydrous 1,2-dichloroethane (12 ml) was added rhodium(II) acetate (2 mg) under refluxing. After refluxing for 20 minutes, the reaction mixture was cooled and evaporated in vacuo to give a residue. The residue was dissolved in anhydrous benzene (10 ml) and then evaporated. This operation was repeated once again and the residue was dried in vacuo to give 4-nitrobenzyl (4R,5R,6S)-6-[(1R)-1-hydroxyethyl]-4-methyl-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate. The compound obtained above was dissolved in anhydrous acetonitrile (15 ml) and cooled to 0 °C under an atmosphere of nitrogen. To this solution were added N,N-diisopropyl-N-ethylamine (0.32 ml) and diphenyl phosphorochloridate (0.33 ml) successively, and the solution was stirred at 0 °C for 40 minutes. To the resulting solution were added dropwise a solution of (2S,4S)-4-mercapto-2-(1-methyl-1H-tetrazol-5-yl)thiomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (0.76 g) in anhydrous acetonitrile (3 ml) and N,N-diisopropyl-N-ethylamine (0.32 ml) with stirring at 0-2 °C, and the stirring was continued at the same temperature for 2 hours. Ethyl acetate (50 ml) was added to the reaction mixture. The mixture was washed twice with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and evaporated in vacuo. The resulting residue was chromatographed on silica gel (100 g) eluting with a mixture of dichloromethane and acetone (5:1, V/V). The fractions containing the desired compound were collected and evaporated in vacuo to give 4-nitrobenzyl (4R,5S,6S)-3-[(2S,4S)-2-(1-methyl-1H-tetrazol-5-yl)thiomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-yl]thio-4-methyl-6-[(1R)-1-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (0.81 g).

IR (Neat) : 1765, 1710-1700, 1660, 1610, 1525, 1350 cm^{-1}

NMR ($CDCl_3$, δ) : 1.39 (3H, d, J=7Hz), 1.36 (3H, d, J=7Hz), 1.63 (1H, m), 3.20-3.42 (2H, m), 3.93 (3H, s), 4.10-4.40 (4H, m), 5.13-5.66 (4H, m), 7.66 (4H, d, J=8Hz), 8.26 (4H, d, J=8Hz)

The following compounds were obtained in substantially the same manner as that of Example 26.

Example 27

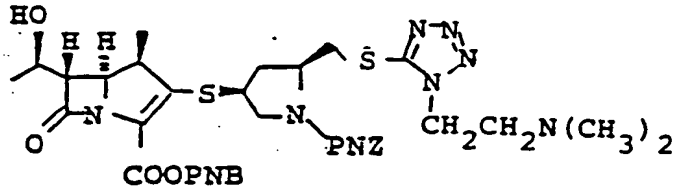


4-Nitrobenzyl (4R,5S,6S)-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-3-[{(2S,4S)-1-(4-nitrobenzyloxycarbonyl)-2-(1,3,4-thiadiazol-2-yl)thiomethyl}pyrrolidin-4-ylthio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

IR (Nujol) : 1760-1740, 1670-1650, 1610, 1515 cm^{-1}

NMR ($CDCl_3$, δ) : 1.28 (3H, d, J = 7Hz), 1.38 (3H, d, J = 7Hz), 1.62-1.88 (2H, m), 5.22-5.52 (4H, m), 7.41-7.83 (4H, m), 8.23 (4H, d, J = 8Hz)

Example 28

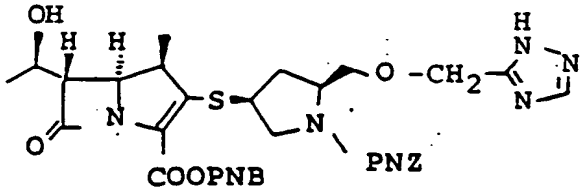


4-Nitrobenzyl (4R,5S,6S)-3-[(2S,4S)-2-[1-{2-(N,N-dimethylamino)ethyl}-1H-tetrazol-5-yl]thiomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-ylthio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

IR (Nujol) : 1765, 1700, 1605, 1520, 1350 cm^{-1}

NMR ($CDCl_3$, δ) : 1.27 (3H, d, J = 6Hz), 1.36 (3H, d, J = 6Hz), 1.73-1.96 (4H, m), 2.25 (6H, s), 2.56-2.93 (3H, m), 5.20-5.47 (4H, m), 8.25 (4H, d, J = 8Hz)

Example 29

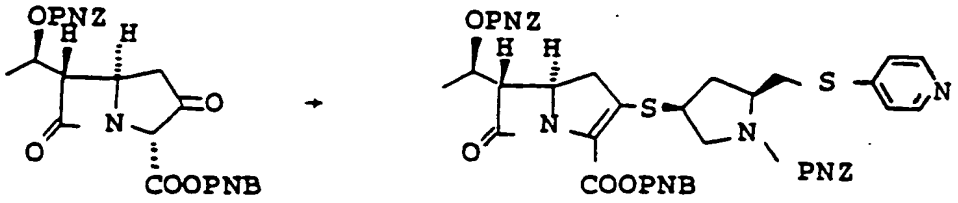


4-Nitrobenzyl (4R,5S,6S)-6-[(1R)-1-hydroxyethyl]-4-methyl-3-[(2S,4S)-1-(4-nitrobenzyloxycarbonyl)-2-{(2H-1,2,4-triazol-3-ylmethyl)oxymethyl}pyrrolidin-4-yl]thio-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

IR (CH_2Cl_2) : 3200-3400, 1765, 1760-1710, 1610 cm^{-1}

NMR ($CDCl_3$, δ) : 1.1-1.4 (6H, m), 2.3-2.7 (1H, m), 4.71 (2H, s), 5.1-5.6 (4H, m), 7.4-7.7 (4H, m), 8.0-8.3 (4H, m)

Example 30

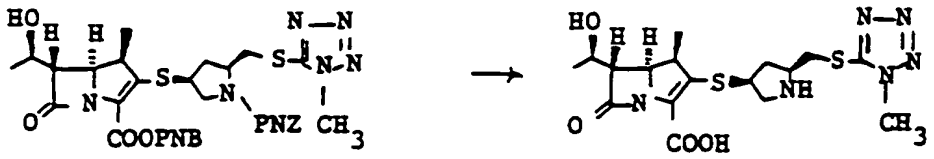


To a solution of 4-nitrobenzyl (2R,5R,6S)-6-[(1R)-1-(4-nitrobenzyloxycarbonyloxy)ethyl]-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate(1.2 g) in dry dichloromethane (40 ml) were added N,N-diisopropyl-N-ethylamine (0.44 ml) and trifluoromethanesulfonic anhydride (0.40 ml) at -40 °C, and the solution was stirred at the same temperature for 15 minutes. To this solution were added N,N-diisopropyl-N-ethylamine (0.63 ml) and a solution of (2S,4S)-4-mercapto-1-(4-nitrobenzyloxycarbonyl)-2-(pyridin-4-ylthiomethyl)-pyrrolidine (1.38 g) in dry dichloromethane (5 ml) successively at the same temperature under an atmosphere of nitrogen, and stirred at ambient temperature for 2 hours. The reaction mixture was washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and evaporated in vacuo to give a residue. The residue was chromatographed on silica gel (100 g) eluting with a mixture of dichloromethane and acetone (4:1 V/V). The fractions containing the desired compound were collected and evaporated in vacuo to give 4-nitrobenzyl (5R,6S)-3-[(2S,4S)-1-(4-nitrobenzyloxycarbonyl)-2-(pyridin-4-ylthiomethyl)pyrrolidin-4-ylthio]-6-[(1R)-1-(4-nitrobenzyloxycarbonyloxy)ethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (0.94 g).

IR (Nujol) : 1780, 1750, 1690, 1610, 1575, 1520, 1350 cm^{-1}

NMR ($CDCl_3$, δ) : 1.42 (3H, d, J=7Hz), 1.80-2.15 (2H, m), 2.35-2.80 (1H, m), 2.85-3.25 (3H, m), 3.25-3.75 (4H, m), 3.90-4.35 (3H, m), 5.00-5.60 (6H, m), 7.35-7.75 (8H, m), 8.10-8.45 (8H, m)

Example 31



A mixture of 4-nitrobenzyl (4R,5S,6S)-3-[(2S,4S)-2-(1-methyl-1H-tetrazol-5-yl)thiomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-yl]thio-4-methyl-6-[(1R)-1-hydroxyethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (0.80 g), 20% palladium hydroxide on carbon (0.5 g), 0.05 M phosphate buffer (pH 6.3, 30 ml) and tetrahydrofuran (30 ml) was stirred for 3 hours under atmospheric pressure of hydrogen at ambient temperature. After the catalyst was filtered off, the filtrate was concentrated under reduced pressure to remove the organic solvent. The residue was washed with ethyl acetate (30 ml x 2) and evaporated in vacuo to remove the organic solvent. The residue was chromatographed on nonionic adsorption resin "Diaion HP-20" (Trademark, made by Mitsubishi Chemical Industries) (20 ml) eluting in turn with water (60 ml) and 10% aqueous acetone solution (120 ml). The fractions containing the desired compound were collected and lyophilized to give (4R,5S,6S)-6-[(1R)-1-hydroxyethyl]-4-methyl-3-[(2S,4S)-2-{(1-methyl-1H-tetrazol-5-yl)-thiomethyl}pyrrolidin-4-ylthio]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (0.23 g).

mp : >165 °C (dec.)

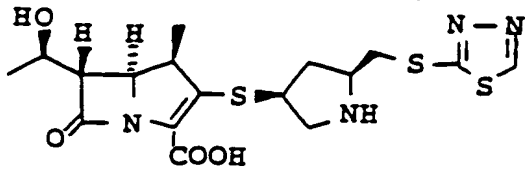
IR (Nujol) : 1760-1750, 1590-1580, 1170 cm^{-1}

NMR (D_2O, δ) : 1.21 (3H, d, J=7Hz), 1.30 (3H, d, J=7Hz), 1.65-2.05 (1H, m), 2.60-3.10 (1H, m), 3.25-3.90 (7H, m), 3.90-4.40 (3H, m), 4.03 (3H, s)

SI Mass : 441 (M^+)

The following compounds were obtained in substantially the same manner as that of Example 31.

Example 32



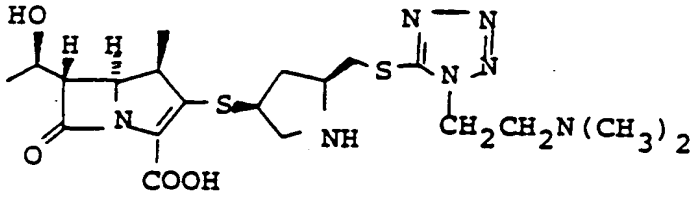
(4R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-4-methyl-7-oxo-3-[(2S,4S)-2-(1,3,4-thiadiazol-2-ylthiomethyl)-pyrrolidin-4-ylthio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

mp : >178 °C (dec.)

IR (Nujol) : 1750, 1585, 1290, 1260 cm^{-1}

NMR (D_2O, δ) : 1.19 (3H, d, J=7Hz), 1.27 (3H, d, J=7Hz), 1.60-2.10 (2H, m), 2.10-3.03 (2H, m), 9.40 (1H, s)

Example 33



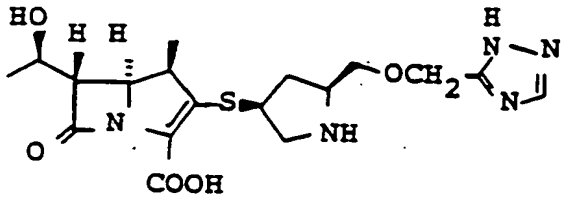
(4R,5S,6S)-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-3-[(2S,4S)-2-[1-{2-(N,N-dimethylamino)ethyl}-1H-tetrazol-5-yl]thiomethylpyrrolidin-4-ylthio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

mp : 163-168 °C (dec.)

IR (Nujol) : 1650, 1590-1580, 1290-1260 cm^{-1}

NMR (D_2O, δ) : 1.28 (3H, d, J=7Hz), 1.27 (3H, d, J=7Hz), 1.53-1.95 (2H, m), 2.64 (6H, s), 2.20-3.04 (2H, m)

Example 34



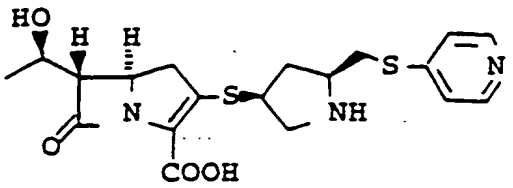
(4R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-4-methyl-7-oxo-3-[(2S,4S)-2-{(2H-1,2,4-triazol-3-ylmethyl)-oxymethyl}pyrrolidin-4-ylthio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

IR (KBr) : 1740-1760, 1580 cm^{-1}

NMR (D_2O, δ) : 1.19 (3H, d, J=8Hz), 1.28 (3H, d, J=6Hz), 2.5-2.9 (1H, m), 8.40 (1H, s)

SI Mass : 424 ($M^+ + 1$)

Example 35



(5R,6S)-6-[(1R)-1-Hydroxyethyl]-7-oxo-3-[(2S,4S)-2-(pyridin-4-ylthiomethyl)pyrrolidin-4-ylthio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

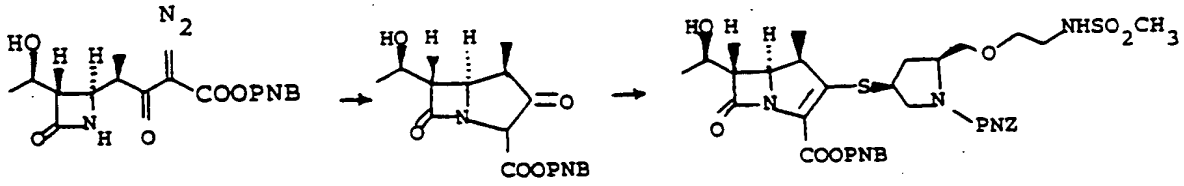
mp : >184 • C (dec.)

IR (Nujol) : 1770-1760, 1580, 1250-1220 cm^{-1}

NMR (DMSO-d_6, δ) : 1.11 (3H, d, J = 7Hz), 1.36-1.50 (1H, m), 2.72-2.90 (1H, m), 7.22-7.32 (2H, m), 8.32-8.40 (2H, m)

SI Mass : 420 (M^+-2)

Example 36

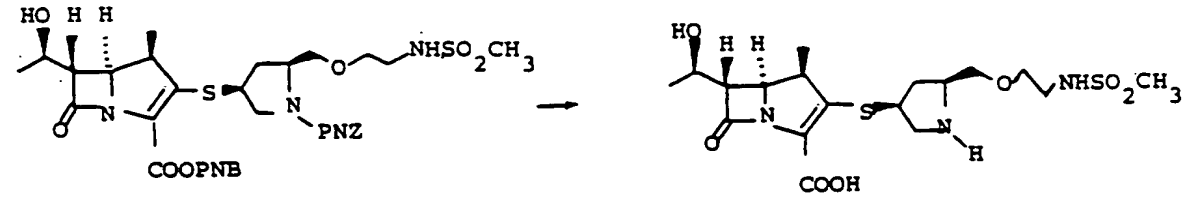


4-Nitrobenzyl (4R,5S,6S)-6-[(1R)-1-hydroxyethyl]-3-[(2S,4S)-2-{2-(methanesulfonylamino)-ethyloxymethyl}-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-yl]thio-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (0.60 g) was obtained by reacting 4-nitrobenzyl (4R)-2-diazo-4-[(2R,3S)-3-{(1R)-1-hydroxyethyl}-4-oxoazetidin-2-yl]-3-oxopentanoate (0.60 g) with (2S,4S)-4-mercapto-2-[2-(methanesulfonylamino)ethyloxymethyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (0.52 g) in substantially the same manner as that of Example 2.

IR ($CHCl_3$) : 1765, 1705-1695 cm^{-1}

NMR ($CDCl_3$, δ) : 1.28 (3H, d, J = 7Hz), 1.36 (3H, d, J = 7Hz), 2.95 (3H, s)

Example 37



(4R,5S,6S)-6-[(1R)-1-Hydroxyethyl]-3-[(2S,4S)-2-{2-(methanesulfonylamino)ethyl}oxymethyl]pyrrolidin-4-yl]thio-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (0.23 g) was obtained by hydrogenating 4-nitrobenzyl (4R,5S,6S)-6-[(1R)-1-hydroxyethyl]-3-[(2S,4S)-2-{2-(methanesulfonylamino)-ethyloxymethyl}-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-yl]thio-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-

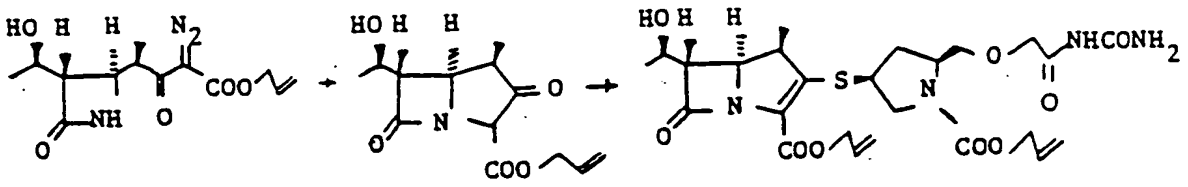
ene-2-carboxylate (0.60 g) in substantially the same manner as that of Example 4.

mp : 160 °C (dec.)

IR (KBr) : 1755-1730 cm^{-1}

NMR (D_2O, δ) : 1.20 (3H, d, J = 7Hz), 1.28 (3H, d, J = 7Hz), 3.08 (3H, s)

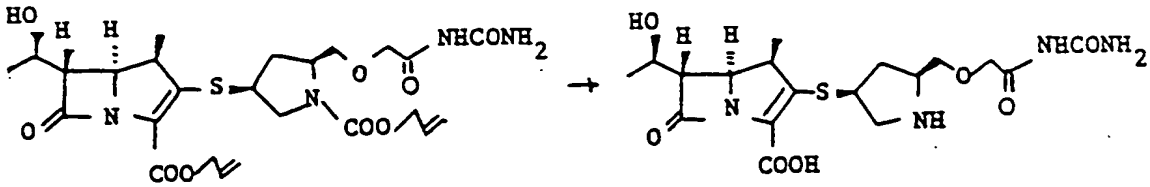
Example 38



To a solution of allyl (4R)-2-diazo-4-[(2R,3S)-3-{(1R)-1-hydroxyethyl}-4-oxoazetidin-2-yl]-3-oxopentanoate (0.36 g) in dichloromethane (2.25 ml) was added rhodium(II) octanoate (6 mg) under reflux. After refluxing for 20 minutes, to the solution was added rhodium(II) octanoate (6 mg). The mixture was refluxed for 40 minutes. The reaction mixture was cooled and evaporated in vacuo to give a residue. The residue was dissolved in anhydrous acetonitrile (4.5ml) and then evaporated. This operation was repeated once again and the resulting residue was dried in vacuo to give allyl (4R,5R,6S)-6-[(1R)-1-hydroxyethyl]-4-methyl-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate. The residue containing the compound obtained above was dissolved in anhydrous acetonitrile (4.5 ml) and cooled to 0 - 5 °C under an atmosphere of nitrogen. To this solution were added diphenyl phosphorochloridate (0.35 ml) and N,N-diisopropyl-N-ethylamine (0.32 ml) successively and the solution was stirred at 0-5 °C for 1 hour. To the resulting solution were added dropwise a solution of (2S,4S)-1-allyloxycarbonyl-4-mercapto-2-[(ureidocarbonylmethyl)oxymethyl]-pyrrolidine (0.35 g) in a mixture of dimethylformamide (1 ml) and acetonitrile (3 ml), and N,N-diisopropyl-N-ethylamine (0.35 ml) successively with stirring at 0-5 °C, and the stirring was continued at the same temperature for 3 hours. To a reaction mixture was added ethyl acetate (50 ml) and water (50 ml) with stirring, and the organic layer was separated. The organic layer was dried over magnesium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel (15 g) eluting with a mixture of acetone and dichloromethane (1:9 and then 2:8 V/V). The fractions containing the desired compound were collected and evaporated in vacuo to give allyl (4R,5S,6S)-3-[(2S, 4S)-1-allyloxycarbonyl-2-{(ureidocarbonylmethyl)oxymethyl}pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (160 mg).

IR ($CHCl_3$) : 1760, 1710-1685 cm^{-1}

Example 39



To a solution of allyl (4R,5S,6S)-3-[(2S,4S)-1-allyloxycarbonyl-2-{(ureidocarbonylmethyl)-oxymethyl}pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (0.23 g) in a mixture of tetrahydrofuran (11.5ml) and water (2.3ml) were added triphenylphosphine (23mg),morpholine (0.12ml), formic acid (0.05 ml), and tetrakis(triphenylphosphine)palladium(0) (26 mg) successively with stirring under ice-cooling. The mixture was stirred at the same temperature for 1 hour and at ambient temperature for 2 hours, and poured into a mixture of ethyl acetate (50 ml) and water (50 ml). The aqueous layer was separated and washed 2 times with ethyl acetate (50 ml). This aqueous layer was

concentrated in vacuo to remov the organic solvent. The residue was chromatographed on nonionic adsorption resin. "Diaion HP-20" (mad by Mitsubishi Chemical Industries)(10ml),eluting in turn with water, and a mixture of acetone and water (5:95 V/V).The fractions containing the desired compound were collected and lyophilized to give (4R,5S, 6S)-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-3-[2S,4S)-2-{(ureidocarbonylmethyl)oxymethyl}pyrrolidin-4-yl]thio-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (0.09 g).

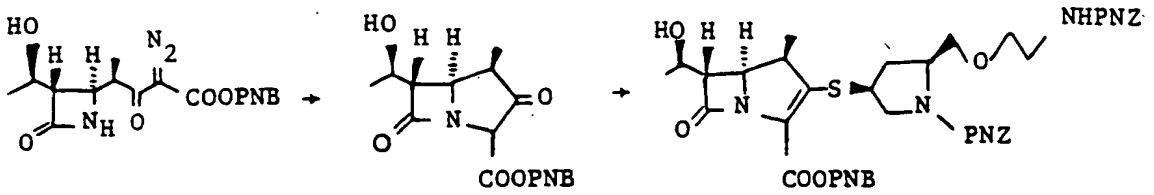
mp : 155 °C (dec.)

IR (Nujol) : 1750-1680 cm^{-1}

NMR ($CDCl_3$, δ) : 1.20 (3H, d, J = 7.5Hz), 1.27 (3H, d, J = 7.5Hz)

SI MS : 443 (M^+ + 1), 426

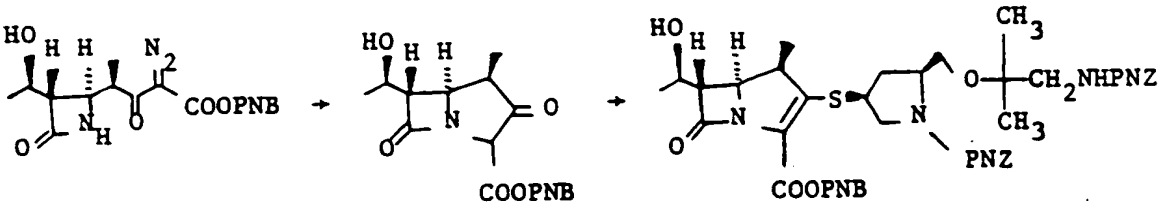
Example 40



To a solution of 4-nitrobenzyl (4R)-2-diazo-4-[(2R,3S)-3-{(1R)-1-hydroxyethyl}-4-oxoazetidin-2-yl]-3-oxopentanoate (0.35 g) in dichloroethane (10 ml) was added rhodium acetate (1 mg) under reflux in a nitrogen stream. The mixture was refluxed for 30 minutes and concentrated under reduced pressure to give 4-nitrobenzyl (4R,5R,6S)-6-[(1R)-1-hydroxyethyl]-4-methyl-3,7-dioxo-1-azabicyclo[3.2.0]heptane-2-carboxylate. The compound obtained above was dissolved in acetonitrile (10 ml). To the solution was added diphenyl phosphorochloridate (0.20 ml) at -10 ~ -5 °C in nitrogen stream and dropwise added N,N-diisopropyl-N-ethylamine (0.20 ml) at the same condition. The mixture was stirred at the same condition for 1 hour. To the solution were added N,N-diisopropyl-N-ethylamine (0.2 ml) and then a solution of (2S,4S)-4-mercapto-1-(4-nitrobenzyloxycarbonyl)-2-[2-(4-nitrobenzyloxycarbonylamino)ethyloxymethyl]pyrrolidine (0.46 g) in acetonitrile (2 ml) at -20 °C. The mixture was stirred at the same temperature for 30 minutes and then at 0-10 °C for 3 hours. The mixture was poured into a mixture of water (60 ml) and ethyl acetate (90 ml). The organic layer was washed with water (90 ml x 2) and brine (90 ml) successively, dried over magnesium sulfate, and concentrated under reduced pressure to give a syrup. The syrup was subjected to a column chromatography on silica gel (20 g) and eluted with a mixture of acetone and dichloromethane (5:95, 10:90, and 15:85, in turn) to give 4-nitrobenzyl (4R,5S,6S)-6-[(1R)-1-hydroxyethyl]-4-methyl-3-[(2S,4S)-1-(4-nitrobenzyloxycarbonyl)-2-{2-(4-nitrobenzyloxycarbonylamino)ethyloxymethyl}pyrrolidin-4-yl]thio-7-oxo-1-azabicyclo[3.2.0]-hept-2-ene-2-carboxylate (0.45 g).

IR ($CHCl_3$) : 1765, 1705 cm^{-1}

Example 41



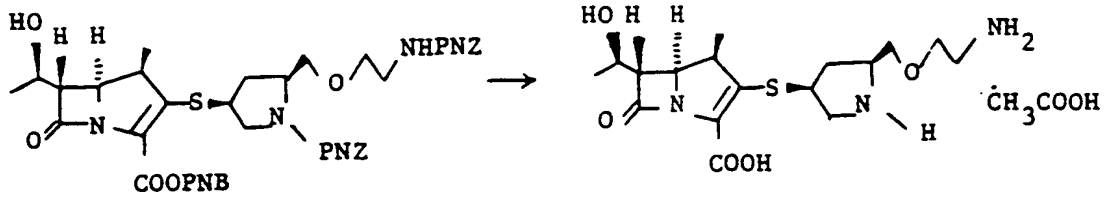
4-Nitrobenzyl (4R,5S,6S)-3-[(2S,4S)-2-[{1,1-dimethyl-2-(4-nitrobenzyloxycarbonylamino)-ethyl}oxymethyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-

azabicyclo[3.2.0]hept-2-ene-2-carboxylate (0.79 g) was obtained by reacting 4-nitrobenzyl (4R)-2-diazo-4-[-(2R,3S)-3-{(1R)-1-hydroxyethyl}-4-oxoazetidin-2-yl]-3-oxopentanoate (0.55 g) with (2S,4S)-2-[{1,1-dimethyl-2-(4-nitrobenzyloxycarbonylamino)ethyl}oxymethyl]-4-mercapto-1-(4-nitrobenzyloxycarbonyl)pyrrolidine (0.70 g) in substantially the same manner as that of Example 40.

IR ($CHCl_3$) : 1765, 1705, 1605 cm^{-1}

NMR ($CDCl_3$, δ) : 1.10 (6H, s), 1.28 (3H, d, J = 7Hz), 1.38 (3H, d, J = 7Hz)

Example 42



A solution of 4-nitrobenzyl (4R,5S,6S)-6-[(1R)-1-hydroxyethyl]-4-methyl-3-[(2S,4S)-1-(4-nitrobenzyloxycarbonyl)-2-{2-(4-nitrobenzyloxycarbonylamino)ethyloxymethyl}pyrrolidin-4-yl]thio-7-oxo-1-azabicyclo-[3.2.0]hept-2-ene-2-carboxylate (0.45 g) in a mixture of tetrahydrofuran (25 ml) and 0.2M acetate buffer (pH 5.8) (25 ml) was stirred in the presence of 20% palladium hydroxide on carbon (0.1 g) under atmospheric pressure of hydrogen at ambient temperature for 8 hours. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to remove tetrahydrofuran. The residual solution was washed with ethyl acetate (40 ml x 2) and the organic solvent was removed by evaporation. The residual solution was subjected to a column chromatography on nonionic adsorption resin, "HP-20" (trademark, made by Mitsubishi Chemical Industries) (20 ml) and eluted with water. The fractions containing the desired compound were collected and lyophilized to give (4R,5S,6S)-3-[(2S,4S)-2-(2-aminoethyloxymethyl)pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid acetate (0.053 g).

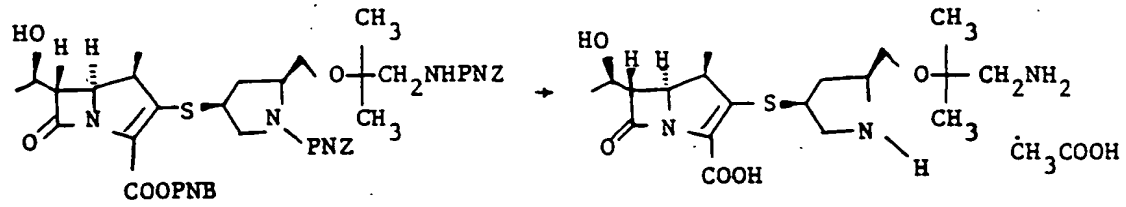
mp : 90 °C (dec.)

IR (KBr) : 1760-1735 cm^{-1}

NMR (D_2O , δ) : 1.23 (3H, d, J = 7Hz), 1.19 (3H, d, J = 7Hz), 1.93 (3H, s)

FD MS : 386

Example 43



(4R,5S,6S)-3-[(2S,4S)-2-{(2-amino-1,1-dimethylethyl)oxymethyl}pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid acetate (0.16 g) was obtained by hydrogenating 4-nitrobenzyl (4R,5S,6S)-3-[(2S,4S)-2-[{1,1-dimethyl-2-(4-nitrobenzyloxycarbonylamino)-ethyl}oxymethyl]-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (0.78 g) in substantially the same manner as that of Example 42.

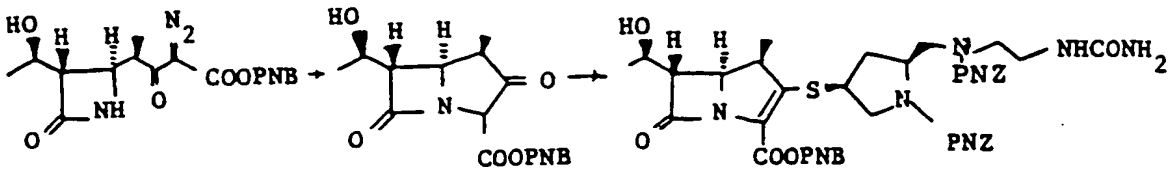
mp : 180 °C (dec.)

IR (KBr) : 1750-1730 cm^{-1}

NMR (D_2O, δ) : 1.1-1.4 (12H, m), 1.78 (3H, s)

SI MS : 414, 343

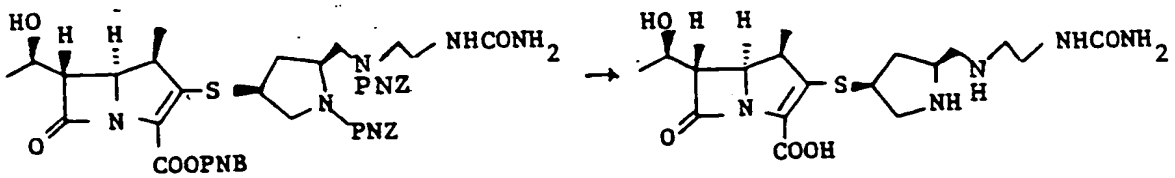
Example 44



To a solution of 4-nitrobenzyl (4R)-2-diazo-4-[(2R, 3S)-3-{(1R)-1-hydroxyethyl}-4-oxoazetidin-2-yl]-3-oxo-pentanoate (0.6 g) in dichloroethane (12 ml) was added rhodium(II) acetate (1 mg) under reflux in a stream of nitrogen. After refluxing for 30 minutes, the mixture was concentrated under reduced pressure to give a syrup. The syrup was dissolved in acetonitrile (12 ml) and cooled to 0~5 °C under an atmosphere of nitrogen. To the solution was added diphenyl phosphorochloridate (0.35 ml) and N,N-diisopropyl-N-ethylamine (0.30 ml) successively and the mixture was stirred at the same condition for 1 hour. To this mixture was added a solution of (2S, 4S)-4-mercapto-1-(4-nitrobenzyloxycarbonyl)-2-[N-(4-nitorbenzyloxycarbonyl)-N-(2-ureidoethyl)aminomethyl]pyrrolidine (0.75 g) in acetonitrile (2 ml) and N,N-diisopropyl-N-ethylamine (0.30 ml) successively at 0~5 °C. The mixture was stirred at 0~5 °C for 3 hours. To the mixture was added ethyl acetate (100 ml). The solution was washed with water (100 ml x 2) and brine (50 ml) successively, dried over magnesium sulfate and concentrated under reduced pressure to give a syrup. The syrup was subjected to a column chromatography on silica gel (15 g) and eluted with a mixture of acetone and dichloromethane (50:50 v/v) to give 4-nitrobenzyl (4R, 5S, 6S)-6-[(1R)-1-hydroxyethyl]-4-methyl-3-[(2S, 4S)-1-(4-nitrobenzyloxycarbonyl)-2-{N-(4-nitrobenzyloxycarbonyl)-N-(2-ureidoethyl)aminomethyl}pyrrolidin-4-yl]thio-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (0.53 g).

IR ($CHCl_3$) : 1765, 1710-1685 cm^{-1}

Example 45



(4R, 5S, 6S)-6-[(1R)-1-Hydroxyethyl]-4-methyl-7-oxo-3-[(2S, 4S)-2-{(2-ureidoethyl)-aminomethyl}pyrrolidin-4-yl]thio-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid (0.11 g) was obtained by hydrogenating 4-nitrobenzyl (4R, 5S, 6S)-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-3-[(2S, 4S)-2-(2-ureidoethyl)aminomethyl-1-(4-nitrobenzyloxycarbonyl)pyrrolidin-4-yl]thio-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (0.52 g) in substantially the same manner as that of Example 42.

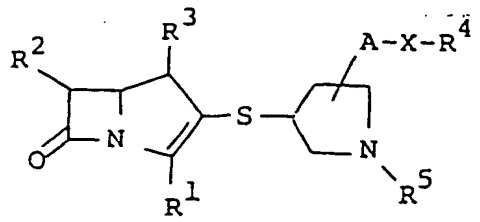
mp : 200 °C (dec.)

IR (KBr) : 1750-1730 cm^{-1}

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A compound of the formula :



(I)

in which

R^1 is carboxy or protected carboxy,

R^2 is hydroxy(C_1-C_4)alkyl or protected hydroxy(C_1-C_4)alkyl,

R^3 is hydrogen or C_1-C_6 alkyl,

R^4 is protected or unprotected hydroxy(C_1-C_6)alkyl; protected or unprotected hydroxy(C_1-C_6)-alkyl having protected or unprotected amino; halo(C_1-C_6)alkyl; protected or unprotected carbamoyl(C_1-C_6)alkyl; protected or unprotected amino(C_1-C_6)alkyl; protected or unprotected ureido(C_1-C_6)alkyl; protected or unprotected ureidocarbonyl(C_1-C_6)alkyl; triazolyl(C_1-C_6)alkyl; saturated or unsaturated 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), or containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), wherein said heterocyclic group may be substituted by suitable substituent(s) selected from C_1-C_6 alkyl, amino, amino(C_1-C_6)alkyl, mono(or di)(C_1-C_6)alkylamino, mono(or di)(C_1-C_6)alkylamino(C_1-C_6)alkyl and imino-protective group; or C_1-C_6 alkylsulfonyl;

R^5 is hydrogen, C_1-C_6 alkanimidoyl or imino-protective group,

A is C_1-C_4 alkylene, and

X is sulfur, oxygen, imino or protected imino,

provided that

when X is oxygen,

then R^4 is not "protected or unprotected ureido(C_1-C_6)alkyl",

and pharmaceutically acceptable salts thereof.

2. A compound of Claim 1, wherein

R^2 is hydroxy(C_1-C_4)alkyl,

R^3 is hydrogen or C_1-C_4 alkyl,

R^4 is carbamoyloxy(C_1-C_4)alkyl; [phenyl(or nitrophenyl)(C_1-C_4)alkoxy]carbonyloxy(C_1-C_4)alkyl; [triphenyl(C_1-C_4)alkoxy](C_1-C_4)alkyl; [tri(C_1-C_4)alkylsilyl]oxy(C_1-C_4)alkyl; hydroxy(C_1-C_4)-alkyl; hydroxy(C_1-C_4)alkyl having amino or phenyl(or nitrophenyl)(C_1-C_4)-alkoxycarbonylamino; dihalo(C_1-C_4)alkyl; carbamoyl(C_1-C_4)alkyl; trihalo(C_1-C_4)-alkanoylcarbamoyl(C_1-C_4)alkyl; N-[bis((C_1-C_4)alkoxyphenyl}(C_1-C_4)alkyl]carbamoyl(C_1-C_4)-alkyl; halosulfonylcarbamoyl(C_1-C_4)alkyl; amino(C_1-C_4)alkyl; N-[phenyl(or nitrophenyl)(C_1-C_4)alkoxycarbonyl]amino(C_1-C_4)alkyl; (C_1-C_4)alkylsulfonylamino(C_1-C_4)alkyl; ureido(C_1-C_4)-alkyl; phenyl(C_1-C_4)alkylureido(C_1-C_4)alkyl; ureidocarbonyl(C_1-C_4)alkyl; phenyl(C_1-C_4)-alkylureidocarbonyl(C_1-C_4)alkyl; triazolyl(C_1-C_4)alkyl; saturated or unsaturated 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), or containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), which may have C_1-C_4 alkyl, N,N-di(C_1-C_4)-alkylamino(C_1-C_4)alkyl or phenyl(or nitrophenyl)(C_1-C_4)alkoxycarbonyl; or (C_1-C_4)-alkylsulfonyl;

R^5 is hydrogen or C_1-C_4 alkanimidoyl, and

A is C_1-C_4 alkylene.

3. A compound of Claim 2, wherein

R^3 is C_1-C_4 alkyl, and

R^4 is carbamoyloxy(C_1-C_4)alkyl; hydroxy(C_1-C_4)alkyl; hydroxy(C_1-C_4)alkyl having amino or nitrophenyl(C_1-C_4)alkoxycarbonylamino; difluoro(C_1-C_4)alkyl; carbamoyl(C_1-C_4)alkyl; amino-

(C_1-C_4)alkyl; N-[nitrophenyl(C_1-C_4)alkoxycarbonylamino(C_1-C_4)alkyl; (C_1-C_4)-alkylsulfonylamino(C_1-C_4)alkyl; ureido(C_1-C_4)alkyl; ureidocarbonyl(C_1-C_4)alkyl; triazolyl(C_1-C_4)alkyl;, tetrazolyl, pyrrolidinyl, thiadiazolyl or tetrazolyl, wherein said heterocyclic groups may have C_1-C_4 alkyl, N,N-di(C_1-C_4)alkylamino(C_1-C_4)alkyl or nitrophenyl(C_1-C_4)-alkoxycarbonyl; or (C_1-C_4)alkylsulfonyl.

4. A compound of Claim 3, wherein
   R^2 is 1-hydroxyethyl,
   R^3 is methyl,
   R^4 is 2-hydroxyethyl, 2-carbamoyloxyethyl, 3-amino-2-hydroxypropyl, difluoromethyl, carbamoylmethyl, 1-carbamoyl-1-methylethyl, 2-aminoethyl, 2-amino-1,1-dimethylethyl, 2-(methylsulfonylamino)ethyl, 2-ureidoethyl, 1,1-dimethyl-2-ureidoethyl, ureidocarbonylmethyl, 1,2,4-triazolylmethyl, pyrrolidinyl, thiadiazolyl, 1-methyl-1H-tetrazolyl, 1-[2-(N,N-dimethylamino)ethyl]-1H-tetrazolyl or methylsulfonyl,
   A is methylene, and
   X is sulfur, oxygen or imino.

5. A compound of Claim 4, which is
(4R,5S,6S)-3-[(2S,4S)-2-{(2-ureidoethyl)thiomethyl}pyrrolidin-4 -yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid.

6. A compound of Claim 4, wherein
   R^4 is 2-hydroxyethyl, 2-carbamoyloxyethyl, carbamoylmethyl, 1-carbamoyl-1-methylethyl, 2-aminoethyl or 2-(methylsulfonylamino)ethyl, and
   X is oxygen.

7. A compound of Claim 6, which is
(4R,5S,6S)-3-[(2S,4S)-2-(2-aminoethyloxymethyl)pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid acetate.

8. A compound of Claim 4, wherein
   R^4 is 2-ureidoethyl or methylsulfonyl, and
   X is imino.

9. A compound of Claim 8, which is
(4R,5S,6S)-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-3-[(2S,4S)-2-{(2-ureidoethyl)aminomethyl}pyrrolidin-4-yl]thio-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid.

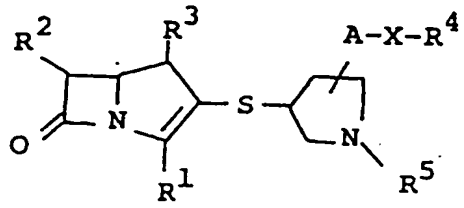
10. A compound of Claim 2, wherein
    R^3 is hydrogen.

11. A compound of Claim 10, wherein
    R^4 is unsaturated 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s).

12. A compound of Claim 11, wherein
    R^2 is 1-hydroxyethyl,
    R^4 is pyridyl,
    R^5 is hydrogen,
    A is methylene, and
    X is sulfur.

13. A compound of Claim 12, which is
(5R,6S)-6-[(1R)-1-hydroxyethyl]-7-oxo-3-[(2S,4S)-2-(pyridin-4-ylthiomethyl)pyrrolidin-4-ylthio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid.

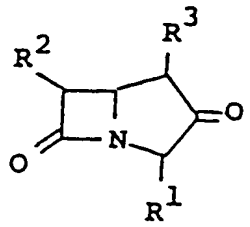
14. A process for the preparation of a compound of the formula :



(I)

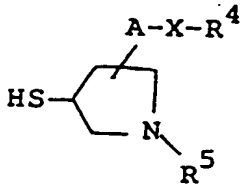
in which R^1 to R^5, A and X are defined as in claim 1 and salts thereof, which comprises

(a) reacting a compound of the formula :



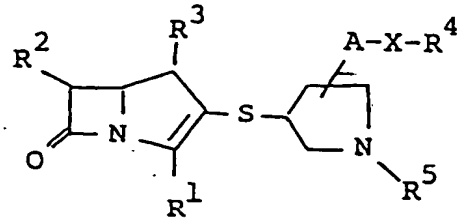
(II)

wherein R^1, R^2 and R^3 are each as defined above, or a reactive derivative at the oxo group thereof or salts thereof with a compound of the formula :



(III)

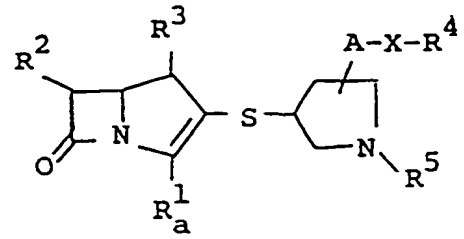
wherein R^4, R^5, A and X are each as defined above, or salts thereof to give a compound of the formula :



(I)

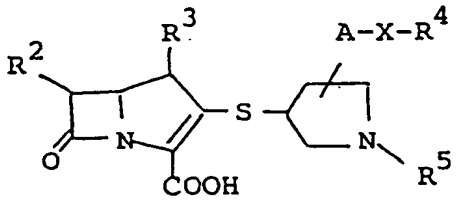
wherein R^1, R^2, R^3, R^4, R^5, A and X are each as defined above, or salts thereof; and

(b) subjecting a compound of the formula :



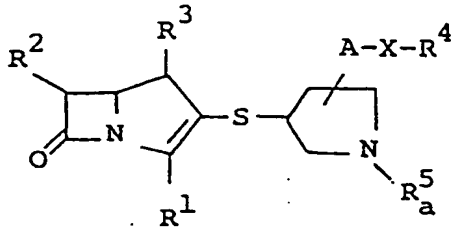
(Ia)

wherein R^2, R^3, R^4, R^5, A and X are each as defined above, and
R_a^1 is protected carboxy,
or salts thereof to elimination reaction of the carboxy-protective group on R_a^1 to give a compound of the formula :



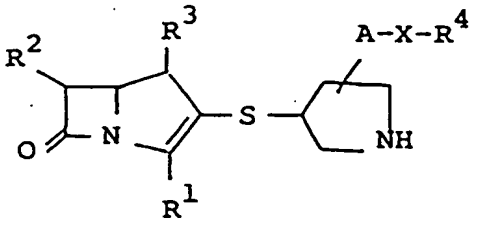
(Ib)

wherein R^2, R^3, R^4, R^5, A and X are each as defined above,
or salts thereof; and
(c) subjecting a compound of the formula :



(Ic)

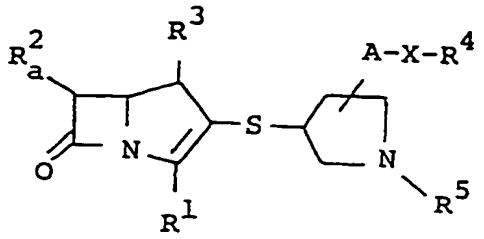
wherein R^1, R^2, R^3, R^4, A and X are each as defined above, and
R_a^5 is imino-protective group,
or salts thereof to elimination reaction of the imino-protective group of R_a^5 to give a compound of the formula :



(Id)

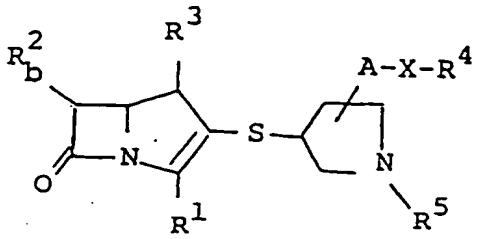
wherein R^1, R^2, R^3, R^4, A and X are each as defined above,
or salts thereof;
and

(d) subjecting a compound of the formula :



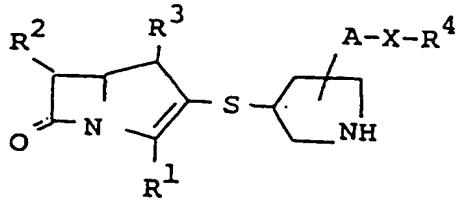
(Ie)

wherein R^1, R^3, R^4, R^5, A and X are each as defined above, and
R^2_a is protected hydroxy(C_1-C_6)alkyl,
or salts thereof to elimination reaction of the hydroxy-protective group on R^2_a to give a compound of the formula :



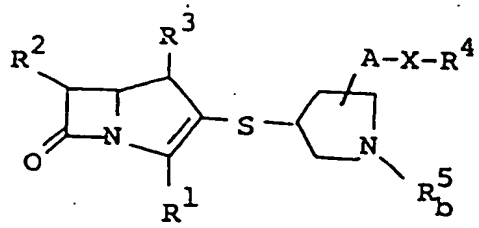
(If)

wherein R^1, R^3, R^4, R^5, A and X are each as defined above, and
R^2_b is hydroxy(C_1-C_6)alkyl,
or salts thereof;
and
(e) reacting a compound of the formula :



(Id)

wherein R^1, R^2, R^3, R^4, A and X are each as defined above,
or salts thereof with C_1-C_6 alkanimidoylating agent to give a compound of the formula :



(Ig)

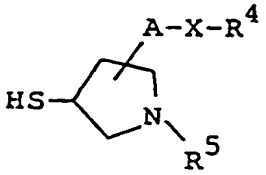
wherein R^1, R^2, R^3, R^4, A and X are each as defined above, and
R^5_b is C_1-C_6 alkanimidoyl,
or salts thereof.

15. A pharmaceutical composition comprising, as an active ingredient, a compound of claim 1, in admixture with a pharmaceutically acceptable carrier or excipient.

16. A compound of claim 1 for use as a medicament.

17. A compound of claim 1 for use in treatment of infectious diseases.

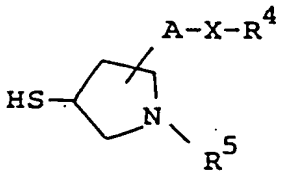
18. A compound of the formula :



(III)

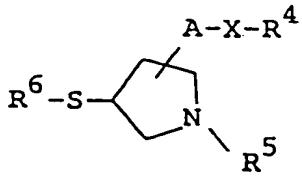
in which R^4, R^5, A and X are each as defined above,
or salts thereof.

19. A process for the preparation of a compound of the formula :



(III)

in which R^4, R^5, A and X are each as defined above,
or salts thereof, which comprises subjecting a compound of the formula :

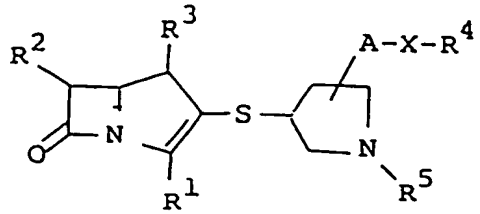


(IIIa)

in which R^4, R^5, A and X are each as defined above, and
R^6 is mercapto-protective group,
or salts thereof to elimination reaction of the mercapto-protective group of R^6.

Claims for the following Contracting State : ES

1. A process for preparing a compund of the formula:



(I)

in which

R^1 is carboxy or protected carboxy,

R^2 is hydroxy(C_1-C_4)alkyl or protected hydroxy(C_1-C_4)alkyl,

R^3 is hydrogen or C_1-C_6 alkyl,

R^4 is protected or unprotected hydroxy(C_1-C_6)alkyl; protected or unprotected hydroxy(C_1-C_6)-alkyl having protected or unprotected amino; halo(C_1-C_6)alkyl; protected or unprotected carbamoyl(C_1-C_6)alkyl; protected or unprotected amino(C_1-C_6)alkyl; protected or unprotected ureido(C_1-C_6)alkyl; protected or unprotected ureidocarbonyl(C_1-C_6)alkyl; triazolyl(C_1-C_6)alkyl; saturated or unsaturated 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), or containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), wherein said heterocyclic group may be substituted by suitable substituent(s) selected from C_1-C_6 alkyl, amino, amino(C_1-C_6)alkyl, mono(or di)(C_1-C_6)alkylamino, mono(or di)(C_1-C_6)alkylamino(C_1-C_6)alkyl and imino-protective group; or C_1-C_6 alkylsulfonyl;

R^5 is hydrogen, C_1-C_6 alkanimidoyl or imino-protective group,

A is C_1-C_4 alkylene, and

X is sulfur, oxygen, imino or protected imino,

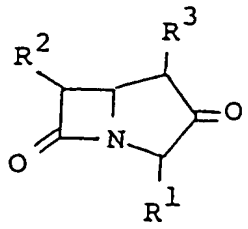
provided that

when X is oxygen,

then R^4 is not "protected or unprotected ureido(C_1-C_6)alkyl",

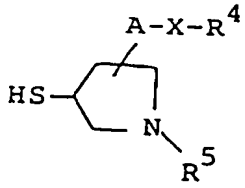
and salts thereof, which comprises

(a) reacting a compound of the formula :



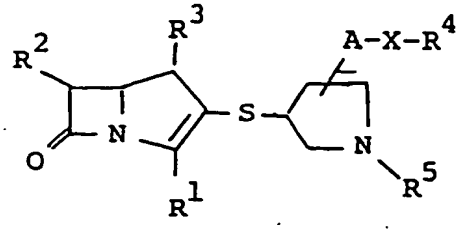
wherein R^1, R^2 and R^3 are each as defined above,

or a reactive derivative at the oxo group thereof or salts thereof with a compound of the formula :



wherein R^4, R^5, A and X are each as defined above,

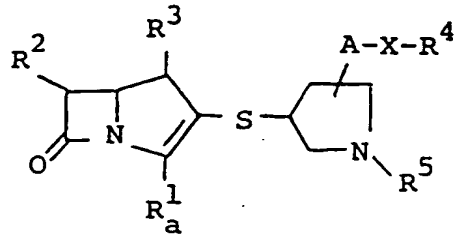
or salts thereof to give a compound of the formula :



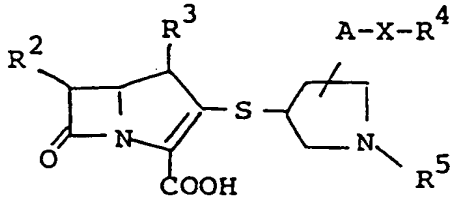
wherein R^1, R^2, R^3, R^4, R^5, A and X are each as defined above,

or salts thereof; and

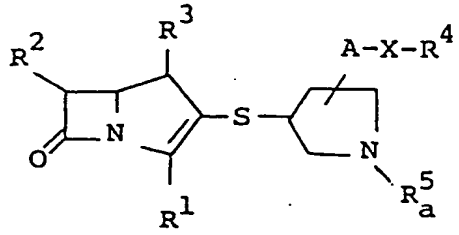
(b) subjecting a compound of the formula :



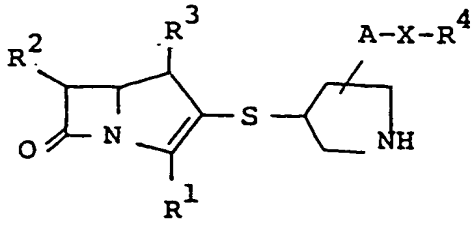
wherein R^2, R^3, R^4, R^5, A and X are each as defined above, and
R_a^1 is protected carboxy,
or salts thereof to elimination reaction of the carboxy-protective group on R_a^1 to give a compound of the formula :



wherein R^2, R^3, R^4, R^5, A and X are each as defined above,
or salts thereof; and
(c) subjecting a compound of the formula :

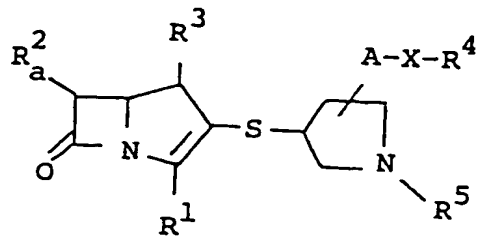


wherein R^1, R^2, R^3, R^4, A and X are each as defined above, and
R_a^5 is imino-protective group,
or salts thereof to elimination reaction of the imino-protective group of R_a^5 to give a compound of the formula :

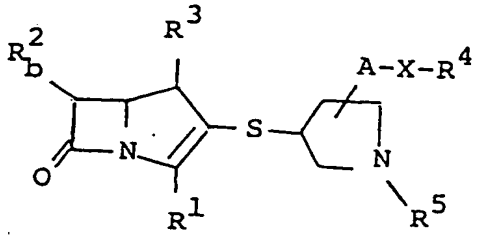


wherein R^1, R^2, R^3, R^4, A and X are each as defined above.

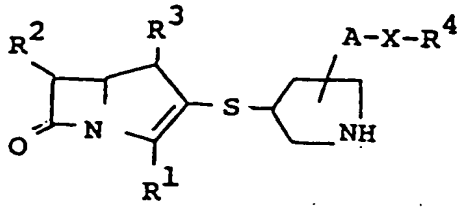
or salts thereof;
and
(d) subjecting a compound of the formula :



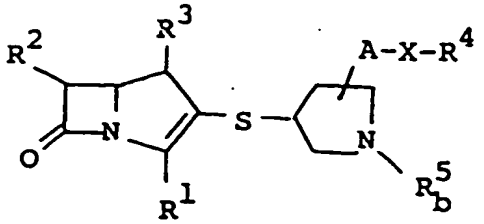
wherein R^1, R^3, R^4, R^5, A and X are each as defined above, and.
R_a^2 is protected hydroxy(C_1-C_6)alkyl,
or salts thereof to elimination reaction of the hydroxy-protective group on R_a^2 to give a compound of the formula :



wherein R^1 R^3, R^4, R^5, A and X are each as defined above, and
R_b^2 is hydroxy(C_1-C_6)alkyl,
or salts thereof;
and
(e) reacting a compound of the formula :



wherein R^1, R^2, R^3, R^4, A and X are each as defined above,
or salts thereof with C_1-C_6 alkanimidoylating agent to give a compound of the formula :



wherein R^1, R^2, R^3, R^4, A and X are each as defined above, and
R^5_0 is C_1-C_6 alkanimidoyl,
or salts thereof.

2. The process according to claim 1 for preparing a compound of formula (I), wherein
R^2 is hydroxy(C_1-C_4)alkyl,
R^3 is hydrogen or C_1-C_4 alkyl,
R^4 is carbamoyloxy(C_1-C_4)alkyl; [phenyl(or nitrophenyl)(C_1-C_4)alkoxy]carbonyloxy(C_1-C_4)alkyl; [triphenyl(C_1-C_4)alkoxy](C_1-C_4)alkyl; [tri(C_1-C_4)alkylsilyl]oxy(C_1-C_4)alkyl; hydroxy(C_1-C_4)-alkyl; hydroxy(C_1-C_4)alkyl having amino or phenyl(or nitrophenyl)(C_1-C_4)-alkoxycarbonylamino; dihalo(C_1-C_4)alkyl; carbamoyl(C_1-C_4)alkyl; trihalo(C_1-C_4)-alkanoylcarbamoyl(C_1-C_4)alkyl; N-[bis{(C_1-C_4)alkoxyphenyl}(C_1-C_4)alkyl]carbamoyl(C_1-C_4)-alkyl; halosulfonylcarbamoyl(C_1-C_4)alkyl; amino(C_1-C_4)alkyl; N-[phenyl(or nitrophenyl)(C_1-C_4)alkoxycarbonyl]amino(C_1-C_4)alkyl; (C_1-C_4)alkylsulfonylamino(C_1-C_4)alkyl; ureido(C_1-C_4)alkyl; phenyl(C_1-C_4)alkylureido(C_1-C_4)alkyl; ureidocarbonyl(C_1-C_4)alkyl; phenyl(C_1-C_4)-alkylureidocarbonyl(C_1-C_4)alkyl; triazolyl(C_1-C_4)alkyl; saturated or unsaturated 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), or containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), which may have C_1-C_4 alkyl, N,N-di(C_1-C_4)-alkylamino(C_1-C_4)alkyl or phenyl(or nitrophenyl)(C_1-C_4)alkoxycarbonyl; or (C_1-C_4)-alkylsulfonyl;
R^5 is hydrogen or C_1-C_4 alkanimidoyl, and
A is C_1-C_4 alkylene.

3. The process according to claim 2 wherein
R^3 is C_1-C_4 alkyl, and
R^4 is carbamoyloxy(C_1-C_4)alkyl; hydroxy(C_1-C_4)alkyl; hydroxy(C_1-C_4)alkyl having amino or nitrophenyl(C_1-C_4)alkoxycarbonylamino; difluoro(C_1-C_4)alkyl; carbamoyl(C_1-C_4)alkyl; amino-(C_1-C_4)alkyl; N-[nitrophenyl(C_1-C_4)alkoxycarbonylamino(C_1-C_4)alkyl; (C_1-C_4)-alkylsulfonylamino(C_1-C_4)alkyl; ureido(C_1-C_4)alkyl; ureidocarbonyl(C_1-C_4)alkyl; triazolyl(C_1-C_4)alkyl;, tetrazolyl, pyrrolidinyl, thiadiazolyl or tetrazolyl, wherein said heterocyclic groups may have C_1-C_4 alkyl, N,N-di(C_1-C_4)alkylamino(C_1-C_4)alkyl or nitrophenyl(C_1-C_4)-alkoxycarbonyl; or (C_1-C_4)alkylsulfonyl.

4. The process according to claim 3, wherein
R^2 is 1-hydroxyethyl,
R^3 is methyl,
R^4 is 2-hydroxyethyl, 2-carbamoyloxyethyl, 3-amino-2-hydroxypropyl, difluoromethyl, carbamoyl-methyl, 1-carbamoyl-1-methylethyl, 2-aminoethyl, 2-amino-1,1-dimethylethyl, 2-(methylsulfonylamino)ethyl, 2-ureidoethyl, 1,1-dimethyl-2-ureidoethyl, ureidocarbonyl-methyl, 1,2,4-triazolylmethyl, pyrrolidinyl, thiadiazolyl, 1-methyl-1H-tetrazolyl, 1-[2-(N,N-dimethylamino)ethyl]-1H-tetrazolyl or methylsulfonyl,
A is methylene, and
X is sulfur, oxygen or imino.

5. The process according to claim 4 for preparing the compound (4R,5S,6S)-3-[(2S,4S)-2-{(2-ureidoethyl)thiomethyl}-pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid.

6. The process according to claim 4, wherein
R^4 is 2-hydroxyethyl, 2-carbamoyloxyethyl, carbamoylmethyl, 1-carbamoyl-1-methylethyl, 2-aminoethyl or 2-(methylsulfonylamino)ethyl, and
X is oxygen.

7. The process according to claim 6, for preparing the compound (4R,5S,6S)-3-[(2S,4S)-2-(2-aminoethyloxymethyl)-pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid acetate.

8. The process according to claim 4, wherein
   R^4 is 2-ureidoethyl or methylsulfonyl, and
   X is imino.

9. The process according to claim 8 for preparing the compound (4R,5S,6S)-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-3-[(2S,4S)-2-{(2-ureidoethyl)aminomethyl}pyrrolidin-4-yl]thio-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid.

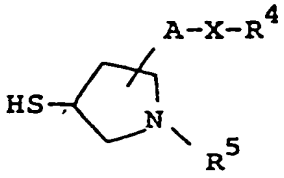
10. The process according to claim 2, wherein R^3 is hydrogen.

11. The process according to claim 10, wherein
    R^4 is unsaturated 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s).

12. The process according to claim 11, wherein
    R^2 is 1-hydroxyethyl,
    R^4 is pyridyl,
    R^5 is hydrogen,
    A is methylene, and
    X is sulfur.

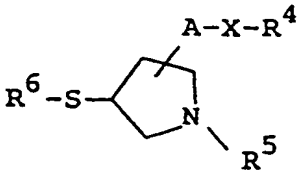
13. The process according to claim 12 for preparing the compound (5R,6S)-6-[(1R)-1-hydroxyethyl]-7-oxo-3-[(2S,4S)-2-(pyridin-4-ylthiomethyl)pyrrolidin-4-ylthio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid.

14. A process for the preparation of a compound of the formula :



(III)

in which R^4, R^5, A and X are each as defined above,
or salts thereof, which comprises subjecting a compound of the formula :

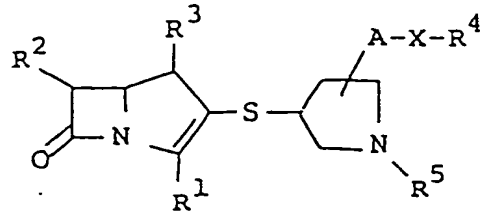


(IIIa)

in which R^4, R^5, A and X are each as defined above, and
R^6 is mercapto-protective group,
or salts thereof to elimination reaction of the mercapto-protective group of R^6.

Claims for the following Contracting State : GR

1. A process for preparing a compund of the formula:



(I).

in which

R^1 is carboxy or protected carboxy,

R^2 is hydroxy(C_1-C_4)alkyl or protected hydroxy(C_1-C_4)alkyl,

R^3 is hydrogen or C_1-C_6 alkyl,

R^4 is protected or unprotected hydroxy(C_1-C_6)alkyl; protected or unprotected hydroxy(C_1-C_6)-alkyl having protected or unprotected amino; halo(C_1-C_6)alkyl; protected or unprotected carbamoyl(C_1-C_6)alkyl; protected or unprotected amino(C_1-C_6)alkyl; protected or unprotected ureido(C_1-C_6)alkyl; protected or unprotected ureidocarbonyl(C_1-C_6)alkyl; triazolyl(C_1-C_6)alkyl; saturated or unsaturated 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), or containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), wherein said heterocyclic group may be substituted by suitable substituent(s) selected from C_1-C_6 alkyl, amino, amino(C_1-C_6)alkyl, mono (or di)(C_1-C_6)alkylamino, mono(or di)(C_1-C_6)alkylamino(C_1-C_6)alkyl and imino-protective group; or C_1-C_6 alkylsulfonyl;

R^5 is hydrogen, C_1-C_6 alkanimidoyl or imino-protective group,

A is C_1-C_4 alkylene, and

X is sulfur, oxygen, imino or protected imino,

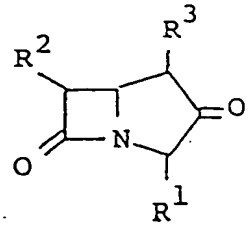
provided that

when X is oxygen,

then R^4 is not "protected or unprotected ureido(C_1-C_6)alkyl",

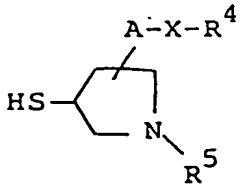
and salts thereof, which comprises

(a) reacting a compound of the formula :



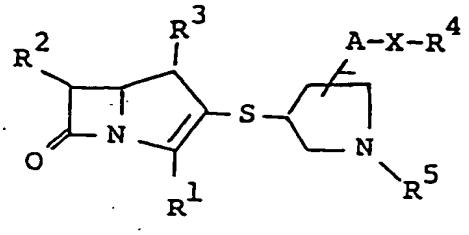
wherein R^1, R^2 and R^3 are each as defined above,

or a reactive derivative at the oxo group thereof or salts thereof with a compound of the formula :

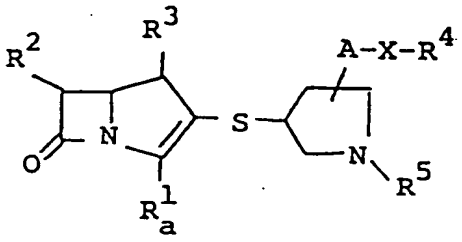


wherein R^4, R^5, A and X are each as defined above,

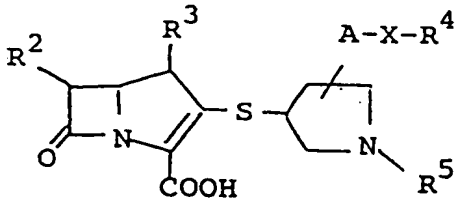
or salts thereof to give a compound of the formula :



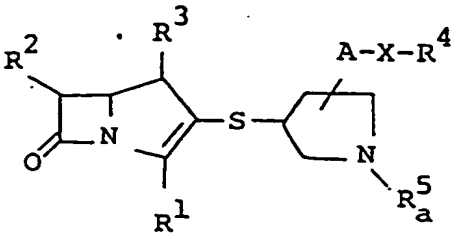
wherein R^1, R^2, R^3, R^4, R^5, A and X are each as defined above,
or salts thereof; and
(b) subjecting a compound of the formula :



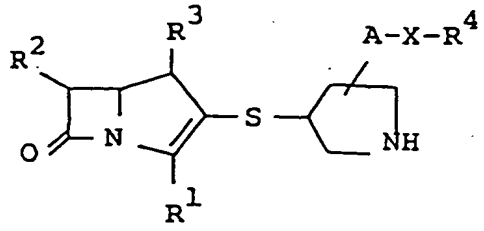
wherein R^2, R^3, R^4, R^5, A and X are each as defined above, and
R_a^1 is protected carboxy,
or salts thereof to elimination reaction of the carboxy-protective group on R_a^1 to give a compound of the formula :



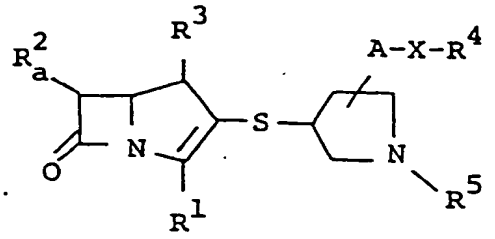
wherein R^2, R^3, R^4, R^5, A and X are each as defined above,
or salts thereof; and
(c) subjecting a compound of the formula :



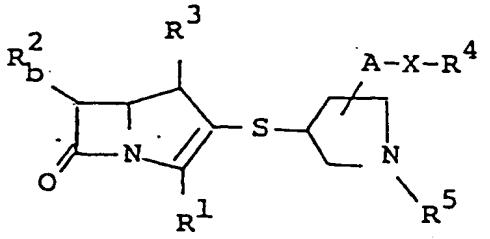
wherein R^1, R^2, R^3, R^4, A and X are each as defined above, and
R_a^5 is imino-protective group,
or salts thereof to elimination reaction of the imino-protective group of R_a^5 to give a compound of the formula :



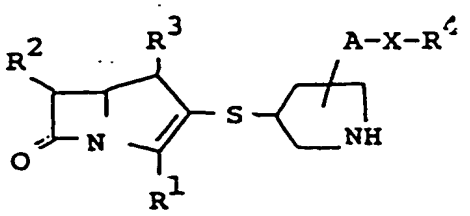
wherein R^1, R^2, R^3, R^4, A and X are each as defined above,
or salts thereof;
and
(d) subjecting a compound of the formula :



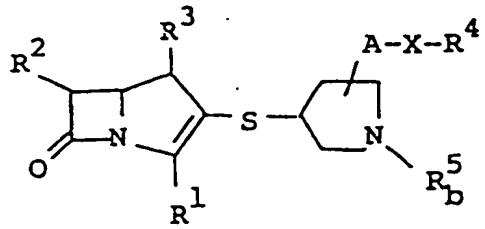
wherein R^1, R^3, R^4, R^5, A and X are each as defined above, and
R^2_a is protected hydroxy(C_1-C_6)alkyl,
or salts thereof to elimination reaction of the hydroxy-protective group on R^2_a to give a compound of the formula :



wherein R^1, R^3, R^4, R^5, A and X are each as defined above, and
R^2_b is hydroxy(C_1-C_6)alkyl,
or salts thereof;
and
(e) reacting a compound of the formula :



wherein R^1, R^2 R^3 R^4, A and X are each as defined above,
or salts thereof with C_1-C_6 alkanimidoylating agent to give a compound of the formula :



wherein R^1, R^2, R^3, R^4, A and X are each as defined above, and
R^5_b is C_1-C_6 alkanimidoyl,
or salts thereof.

2. The process according to claim 1 for preparing a compound of formula (I), wherein
R^2 is hydroxy(C_1-C_4)alkyl,
R^3 is hydrogen or C_1-C_4 alkyl,
R^4 is carbamoyloxy(C_1-C_4)alkyl; [phenyl(or nitrophenyl)(C_1-C_4)alkoxy]carbonyloxy(C_1-C_4)alkyl; [triphenyl(C_1-C_4)alkoxy](C_1-C_4)alkyl; [tri(C_1-C_4)alkylsilyl]oxy(C_1-C_4)alkyl; hydroxy(C_1-C_4)-alkyl; hydroxy(C_1-C_4)alkyl having amino or phenyl(or nitrophenyl)(C_1-C_4)-alkoxycarbonylamino; dihalo(C_1-C_4)alkyl; carbamoyl(C_1-C_4)alkyl; trihalo(C_1-C_4)-alkanoylcarbamoyl(C_1-C_4)alkyl; N-[bis{(C_1-C_4)alkoxyphenyl}(C_1-C_4)alkyl]carbamoyl(C_1-C_4)-alkyl; halosulfonylcarbamoyl(C_1-C_4)alkyl; amino(C_1-C_4)alkyl; N-[phenyl(or nitrophenyl)(C_1-C_4)alkoxycarbonyl]amino(C_1-C_4)alkyl; (C_1-C_4)alkylsulfonylamino(C_1-C_4)alkyl; ureido(C_1-C_4)alkyl, phenyl(C_1-C_4)alkylureido(C_1-C_4)alkyl; ureidocarbonyl(C_1-C_4)alkyl; phenyl(C_1-C_4)-alkylureidocarbonyl(C_1-C_4)alkyl; triazolyl(C_1-C_4)alkyl; saturated or unsaturated 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s), or containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), which may have C_1-C_4 alkyl, N,N-di(C_1-C_4)-alkylamino(C_1-C_4)alkyl or phenyl(or nitrophenyl)(C_1-C_4)alkoxycarbonyl; or (C_1-C_4)-alkylsulfonyl;
R^5 is hydrogen or C_1-C_4 alkanimidoyl, and
A is C_1-C_4 alkylene.

3. The process according to claim 2 wherein
R^3 is C_1-C_4 alkyl, and
R^4 is carbamoyloxy(C_1-C_4)alkyl; hydroxy(C_1-C_4)alkyl; hydroxy(C_1-C_4)alkyl having amino or nitrophenyl(C_1-C_4)alkoxycarbonylamino; difluoro(C_1-C_4)alkyl; carbamoyl(C_1-C_4)alkyl; amino-(C_1-C_4)alkyl; N-[nitrophenyl(C_1-C_4)alkoxycarbonylamino(C_1-C_4)alkyl; (C_1-C_4)-alkylsulfonylamino(C_1-C_4)alkyl; ureido(C_1-C_4)alkyl; ureidocarbonyl(C_1-C_4)alkyl; triazolyl(C_1-C_4)alkyl;, tetrazolyl, pyrrolidinyl, thiadiazolyl or tetrazolyl, wherein said heterocyclic groups may have C_1-C_4 alkyl, N,N-di(C_1-C_4)alkylamino(C_1-C_4)alkyl or nitrophenyl(C_1-C_4)-alkoxycarbonyl; or (C_1-C_4)alkylsulfonyl.

4. The process according to claim 3, wherein
R^2 is 1-hydroxyethyl,
R^3 is methyl,
R^4 is 2-hydroxyethyl, 2-carbamoyloxyethyl, 3-amino-2-hydroxypropyl, difluoromethyl, carbamoyl-methyl, 1-carbamoyl-1-methlethyl, 2-aminoethyl, 2-amino-1,1-dimethylethyl, 2-(methylsulfonylamino)ethyl, 2-ureidoethyl, 1,1-dimethyl-2-ureidoethyl, ureidocarbonyl-methyl, 1,2,4-triazolylmethyl, pyrrolidinyl, thiadiazolyl; 1-methyl-1H-tetrazolyl, 1-[2-(N,N-dimethylamino)ethyl]-1H-tetrazolyl or methylsulfonyl,
A is methylene, and
X is sulfur, oxygen or imino.

5. The process according to claim 4 for preparing the compound (4R,5S,6S)-3-[(2S,4S)-2-{(2-ureidoethyl)thiomethyl)pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid.

6. The process according to claim 4, wherein
R^4 is 2-hydroxyethyl, 2-carbamoyloxyethyl, carbamoylmethyl, 1-carbamoy1-1-methylethyl, 2-aminoethyl or 2-(methylsulfonylamino)ethyl, and
X is oxygen.

7. The process according to claim 6, for preparing the compound (4R,5S,6S)-3-[(2S,4S)-2-(2-aminoethyloxymethyl)-pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid acetate.

8. The process according to claim 4, wherein
R^4 is 2-ureidoethyl or methylsulfonyl, and
X is imino.

9. The process according to claim 8 for preparing the compound (4R,5S,6S)-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-3-[(2S,4S)-2-{(2-ureidoethyl)aminomethyl]pyrrolidin-4-yl]thiol-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid.

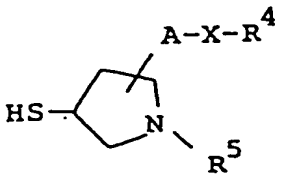
10. The process according to claim 2, wherein R^3 is hydrogen.

11. The process according to claim 10, wherein
R^4 is unsaturated 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s).

12. The process according to claim 11, wherein
R^2 is 1-hydroxyethyl,
R^4 is pyridyl,
R^5 is hydrogen,
A is methylene, and
X is sulfur.

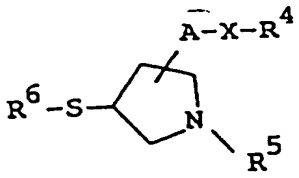
13. The process according to claim 12 for preparing the compound (5R,6S)-6-[(1R)-1-hydroxyethyl]-7-oxo-3-[(2S,4S)-2-(pyridin-4-ylthiomethyl)pyrrolidin-4-ylthio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid.

14. A process for the preparation of a compound of the formula :



(III)

in which R^4, R^5, A and X are each as defined above,
or salts thereof, which comprises subjecting a compound of the formula :



(IIIa)

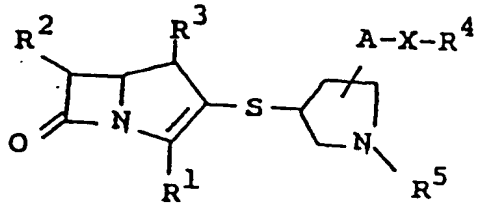
in which R^4, R^5, A and X are each as defined above, and
R^6 is mercapto-protective group,
or salts thereof to elimination reaction of the mercapto-protective group of R^6.

15. Modification of the processes of any of claims 1 to 13, characterized in that a compound prepared by a process according to any of claims 1 to 13 is brought into a pharmaceutically acceptable form by admixture or presentation of said compound with a pharmaceutically acceptable diluent or carrier.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Verbindung der Formel



(I)

worin R^1 Carboxy oder geschütztes Carboxy darstellt, R^2 ist Hydroxy(C_1-C_4)-alkyl oder geschütztes Hydroxy(C_1-C_4)-alkyl, R^3 ist Wasserstoff oder C_1-C_6-Alkyl,
R^4 ist geschütztes oder ungeschütztes Hydroxy(C_1-C_4)-alkyl; geschütztes oder ungeschütztes Hydroxy-(C_1-C_4)-alkyl mit geschütztem oder ungeschütztem Amino; Halo(C_1-C_6)-alkyl; geschütztes oder ungeschütztes Carbamoyl(C_1-C_6)-alkyl; geschütztes oder ungeschütztes Amino(C_1-C_6)-alkyl; geschütztes oder ungeschütztes Ureido(C_1-C_6)-alkyl; geschütztes oder ungeschütztes Ureidocarbonyl(C_1-C_6)-alkyl; Triazolyl(C_1-C_6)-alkyl; eine gesättigte oder ungesättigte 5- oder 6-gliedrige heteromonocyclische Gruppe, die 1 bis 4 Stickstoffatome enthält oder 1 bis 2 Schwefelatome und 1 bis 3 Stickstoffatome, worin die genannte heterocyclische Gruppe substituiert sein kann durch geeignete Substituenten, ausgewählt unter (C_1-C_6)-Alkyl, Amino, Amino(C_1-C_6)-alkyl; Mono-(oder Di-)(C_1-C_6)-alkylamino, Mono-(oder Di-)(C_1-C_6)-alkylamino(C_1-C_6)-alkyl und die Imino-Schutzgruppe; oder C_1-C_6-Alkylsulfonyl;
R^5 ist Wasserstoff, C_1-C_6-Alkanimidoyl oder Imino-Schutzgruppe,
A ist C_1-C_4-Alkylen, und
X ist Schwefel, Sauerstoff, Imino oder geschütztes Imino, vorausgesetzt, daß wenn X Sauerstoff ist, R^4 nicht "geschütztes oder ungeschütztes Ureido(C_1-C_6)-alkyl" ist,
sowie pharmazeutisch annehmbare Salze davon.

2. Verbindung nach Anspruch 1, worin
R^2 die Bedeutung Hydroxy(C_1-C_4)-alkyl hat,
R^3 ist Wasserstoff oder C_1-C_4-Alkyl,
R^4 ist Carbamoyloxy(C_1-C_4)-alkyl; [Phenyl(oder Nitrophenyl)-(C_1-C_4)-alkoxy]carbonyloxy(C_1-C_4)-alkyl; [Triphenyl(C_1-C_4)-alkoxy](C_1-C_4)-alkyl; (Tri(C_1-C_4)-alkylsilyl]-oxy(C_1-C_4)-alkyl; Hydroxy(C_1-C_4)-alkyl; Hydroxy(C_1-C_4)-alkyl mit Amino- oder Phenyl- (oder Nitrophenyl)(C_1-C_4)-alkoxycarbonylamino; Dihalo-(C_1-C_4)-alkyl; Carbamoyl(C_1-C_4)alkyl; Trihalo(C_1-C_4)-alkanoylcarbamoyl(C_1-C_4)alkyl; N-[Bis{(C_1-C_4)-alkoxyphenyl}(C_1-C_4)-alkyl]-carbamoyl(C_1-C_4)-alkyl; Halosulfonylcarbamoyl(C_1-C_4)-alkyl; Amino(C_1-C_4)-alkyl; N-[Phenyl-(oder Nitrophenyl)(C_1-C_4)-alkoxycarbonyl]amino-(C_1-C_4)-alkyl; (C_1-C_4)-Alkylsulfonylamino-(C_1-C_4)-alkyl; Ureido(C_1-C_4)-alkyl; Phenyl(C_1-C_4)-alkylureido(C_1-C_4)-alkyl; Ureidocarbonyl(C_1-C_4)-alkyl; Phenyl(C_1-C_4)-alkylureidocarbonyl(C_1-C_4)-alkyl; Triazolyl(C_1-C_4)alkyl; eine gesättigte oder ungesättigte 5- oder 6-gliedrige heteromonocyclische Gruppe, die 1 bis 4 Stickstoffatome enthält oder 1 bis 2 Schwefelatome und 1 bis 3 Stickstoffatome enthält, die C_1-C_4-Alkyl, N,N-Di(C_1-C_4)-alkylamino(C_1-C_4)-alkyl oder Phenyl- (oder Nitrophenyl-)(C_1-C_4)-alkoxycarbonyl oder (C_1-C_4)-Alkylsulfonyl, haben kann.
R^5 ist Wasserstoff oder C_1-C_6-Alkanimidoyl, und
A ist C_1-C_4-Alkylen.

3. Verbindung nach Anspruch 2, worin
R^3 die Bedeutung C_1-C_4-Alkyl hat, und
R^4 ist Carbamoyloxy(C_1-C_4)-alkyl; Hydroxy(C_1-C_4)-alkyl; Hydroxy(C_1-C_4)-alkyl mit Amino oder Nitroph nyl(C_1-C_4)-alkoxycarbonylamino; Difluor(C_1-C_4)-alkyl; Carbamoyl(C_1-C_4)-alkyl; Amino(C_1-C_4)-alkyl; N-[Nitrophenyl(C_1-C_4)-alkoxycarbonylamino(C_1-C_4)-alkyl; (C_1-C_4)-Alkylsulfonylamino(C_1-C_4)-alkyl; Ureido(C_1-C_4)-alkyl; Ureidocarbonyl(C_1-C_4)-alkyl; Triazolyl(C_1-C_4)-alkyl; Tetrazolyl, Pyrrolidinyl, Thiadiazolyl oder Tetrazolyl, worin die genannten heterocyclischen Gruppen C_1-C_4-Alkyl, N,N-Di(C_1-C_4)-alkylamino-(C_1-C_4)-alkyl oder Nitrophenyl(C_1-C_4)-alkoxycarbonyl haben können; oder (C_1-C_4)-alkylsulfonyl.

4. Verbindung nach Anspruch 3, worin
R^2 die Bedeutung 1-Hydroxyethyl hat,
R^3 ist Methyl,
R^4 ist 2-Hydroxyethyl, 2-Carbamoyloxyethyl, 3-Amino-2-hydroxypropyl, Difluormethyl, Carbamoylmethyl, 1-Carbamoyl-1-methylethyl, 2-Aminoethyl, 2-Amino-1,1-Dimethylethyl, 2-(Methylsulfonylamino)-ethyl, 2-Ureidoethyl,1,1-Dimethyl-2-ureidoethyl, Ureidocarbonylmethyl, 1,2,4-Triazolylmethyl, Pyrrolidinyl, Thiadiazolyl, 1-Methyl-1H-tetrazolyl, 1-[2-(N,N-Dimethylamino)ethyl]-1H-tetrazolyl oder Methylsulfonyl, A ist Methylen, und X ist Schwefel, Sauerstoff oder Imino.

5. Verbindung nach Anspruch 4, die (4R,5S,6S)-3-[(2S,4S)-2-{(2-Ureidoethyl)thiomethyl}-pyrrolidin-4-yl]-thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-en-2-carbonsäure ist.

6. Verbindung nach Anspruch 4, worin R^4 die Bedeutung 2-Hydroxyethyl, 2-Carbamoyloxyethyl, Carbamoylmethyl, 1-Carbamoyl-1-methylethyl, 2-Aminoethyl oder 2-(Methylsulfonylamino)ethyl hat, und X ist Sauerstoff.

7. Verbindung nach Anspruch 6, die (4R,5S,6S)-3-[2S,4S)-(2-Aminoethyloxymethyl)-pyrrolidin-4-yl]thio-6-[-(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-en-2-carbonsäure-Acetat ist.

8. Verbindung nach Anspruch 4, worin R^4 die Bedeutung 2-Ureidoethyl oder Methylsulfonyl hat und X ist Imino.

9. Verbindung nach Anspruch 8, die (4R,5R,6S)-6-[(1R)-1-Hydroxyethyl]-4-methyl-7-oxo-3-[(2S,4S)-2-{2-ureidoethylaminomethyl}pyrrolidin-4-yl]thio-1-azabicyclo[3.2.0]hept-2-en-2-carbonsäure ist.

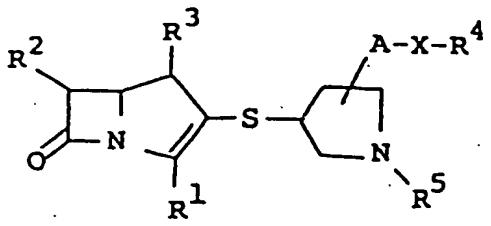
10. Verbindung nach Anspruch 2, worin R^3 Wasserstoff ist.

11. Verbindung nach Anspruch 10, worin R^4 eine ungesättigte 5- oder 6-gliedrige heteromonocyclische Gruppe ist, die 1 bis 4 Stickstoffatom(e) enthält.

12. Verbindung nach Anspruch 11, worin R^2 die Bedeutung 1-Hydroxyethyl hat, R^4 ist Pyridyl, R^5 ist Wasserstoff, A ist Methylen und X ist Schwefel.

13. Verbindung nach Anspruch 12, die (5R,6S)-6-[(1R)-1-Hydroxyethyl]-7-oxo-3-[(2S,4S)-2-(pyridin-4-ylthiomethyl)pyrrolidin-4-ylthio]-1-azabicyclo[3.2.0.]hept-2-en-2-carbonsäure ist.

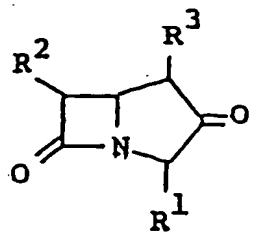
14. Verfahren zur Herstellung einer Verbindung der Formel



(I)

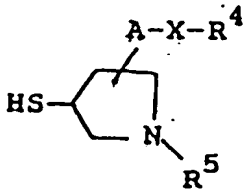
worin R^1 bis R^5, A und X wie in Anspruch 1 definiert sind, sowie Salze davon, gekennzeichnet durch

(a) Reaktion einer Verbindung der Formel



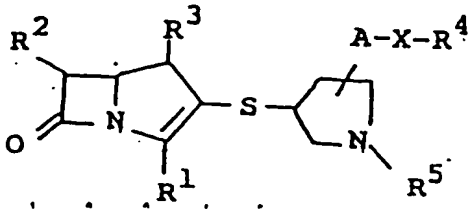
(II)

worin R^1, R^2 und R^3 jeweils wie oben definiert sind oder eines reaktionsfähigen Derivates an der Oxo-Gruppe davon oder Salze davon mit einer Verbindung der Formel



(III)

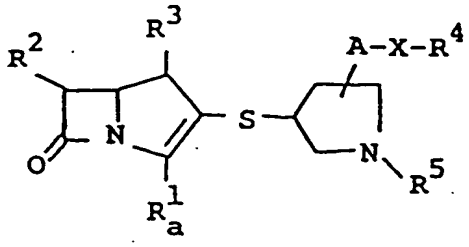
worin R^4, R^5, A und X jeweils wie oben definiert sind, oder Salze davon, um zu einer Verbindung der Formel



(I)

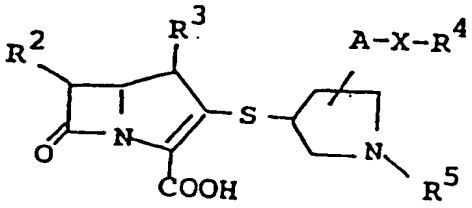
zu gelangen, worin R^1, R^2, R^3, R^4, R^5, A und X jeweils wie oben definiert sind, oder Salze davon; und

(b) Unterwerfen einer Verbindung der Formel



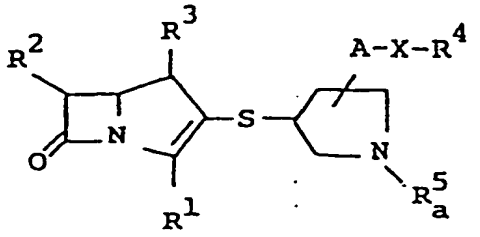
(Ia)

worin R^2, R^3, R^4, R^5, A und X jeweils wie oben definiert sind, und R_a^1, geschütztes Carboxy darstellt, oder Salze davon, einer Eliminierungsreaktion der Carboxyschutzgruppe an R_a^1, um zu einer Verbindung der Formel



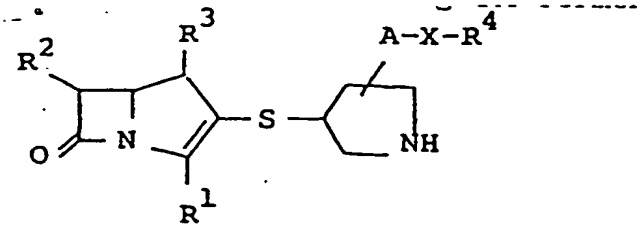
(Ib)

zu gelangen, worin R^2, R^3, R^4, R^5, A und X jeweils wie oben definiert sind, oder Salze davon; und
(c) Unterwerfen einer Verbindung der Formel



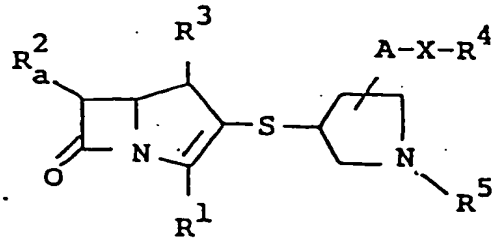
(Ic)

worin R^1, R^2, R^3, R^4, A und X jeweils wie oben definiert sind, und R_a^5 ist eine Imino-Schutzgruppe, oder Salze davon, einer Eliminierungsreaktion der Imino-Schutzgruppe von R_a^5, um zu einer Verbindung der Formel



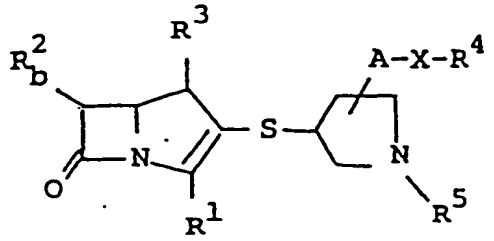
(Id)

zu gelangen, worin R^1, R^2, R^3, R^4, A und X jeweils wie oben definiert sind, oder Salzen davon; und
(d) Unterwerfen einer Verbindung der Formel



(Ie)

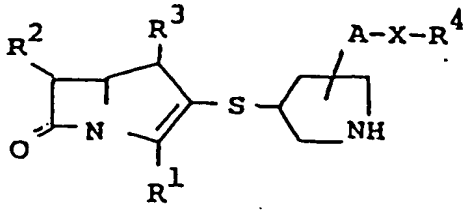
worin R^1, R^3, R^4, R^5, A und X jeweils wie oben definiert sind, und R_a^2 ist geschütztes Hydroxy(C_1-C_6)-alkyl oder Salze davon, einer Eliminierungsreaktion der Hydroxy-Schutzgruppe an R_a^2, um zu einer Verbindung der Formel



(If)

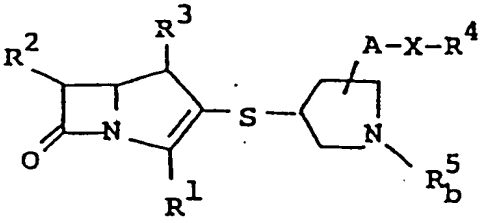
zu gelangen, worin R^1, R^3, R^4, R^5, A und X jeweils wie oben definiert sind und R_b^2 ist Hydroxy(C_1-C_6)-alkyl, oder Salze davon; und

(e) Umsetzung einer Verbindung der Formel



(Id)

worin R^1, R^2, R^3, R^4, A und X jeweils wie oben definiert sind, oder Salze davon mit einem C_1-C_6-Alkanimidoylierungsmittel, um zu einer Verbindung der Formel



(Ig)

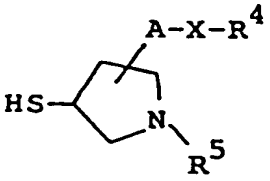
zu gelangen, worin R^1, R^2, R^3, R^4, A und X jeweils wie oben definiert sind, und R_b^5 ist C_1-C_6-Alkanimidoyl, oder Salze davon.

15. Pharmazeutische Zusammensetzung, die als aktiven Bestandteil eine Verbindung nach Anspruch 1 umfaßt im Gemisch mit einem pharmazeutisch annehmbaren Träger oder Exzipienten.

16. Verbindung nach Anspruch 1 zur Verwendung als Medikament.

17. Verbindung nach Anspruch 1 zur Verwendung bei der Behandlung infektiöser Krankheiten.

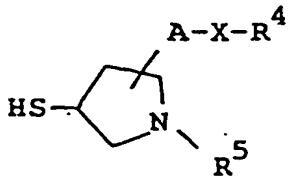
18. Verbindung der Formel



(III)

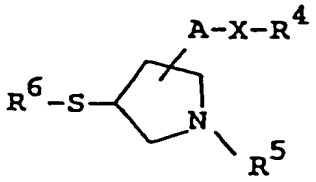
worin R^4, R^5, A und X jeweils wie oben definiert sind oder Salze davon.

19. Verfahren zur Herstellung einer Verbindung der Formel



(III)

worin R^4, R^5, A und X jeweils wie oben definiert sind, oder von Salzen davon, dadurch gekennzeichnet, daß eine Verbindung der allgemeinen Formel

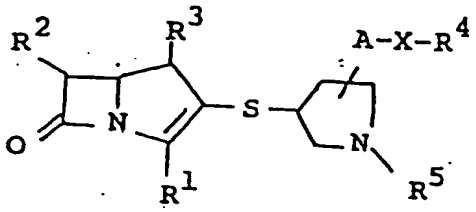


(IIIa)

worin R^4, R^5, A und X jeweils wie oben definiert sind und R^6 eine Mercapto-Schutzgruppe ist, oder Salze davon, einer Eliminierungsreaktion der Mercapto-Schutzgruppe von R^6 unterworfen wird.

Patentansprüche für folgenden Vertragsstaat : ES

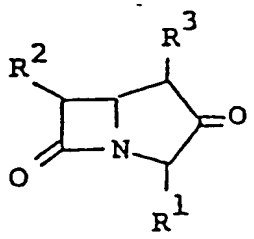
1. Verfahren zur Herstellung einer Verbindung der Formel



(I)

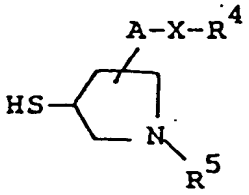
worin R^1 Carboxy oder geschütztes Carboxy darstellt, R^2 ist Hydroxy(C_1-C_4)-alkyl oder geschütztes Hydroxy(C_1-C_4)-alkyl, R^3 ist Wasserstoff oder C_1-C_6-Alkyl,
R^4 ist geschütztes oder ungeschütztes Hydroxy(C_1-C_4)-alkyl; geschütztes oder ungeschütztes Hydroxy-(C_1-C_4)-alkyl mit geschütztem oder ungeschütztem Amino; Halo(C_1-C_6)-alkyl; geschütztes oder ungeschütztes Carbamoyl(C_1-C_6)-alkyl; geschütztes oder ungeschütztes Amino(C_1-C_6)-alkyl; geschütztes oder ungeschütztes Ureido(C_1-C_6)-alkyl; geschütztes oder ungeschütztes Ureidocarbonyl(C_1-C_6)-alkyl; Triazolyl(C_1-C_6)-alkyl; eine gesättigte oder ungesättigte 5- oder 6-gliedrige heteromonocyclische Gruppe, die 1 bis 4 Stickstoffatome enthält oder 1 bis 2 Schwefelatome und 1 bis 3 Stickstoffatome, worin die genannte heterocyclische Gruppe substituiert sein kann durch geeignete Substituenten, ausgewählt unter (C_1-C_6)-Alkyl, Amino, Amino(C_1-C_6)-alkyl; Mono-[oder Di-)(C_1-C_6)-alkylamino, Mono-(oder Di)(C_1-C_6)-alkylamino(C_1-C_6)-alkyl und die Imino-Schutzgruppe; oder C_1-C_6-Alkylsulfonyl;
R^5 ist Wasserstoff, C_1-C_6-Alkanimidoyl oder Imino-Schutzgruppe,
A ist C_1-C_4-Alkylen, und
X ist Schwefel, Sauerstoff, Imino oder geschütztes Imino, vorausgesetzt, daß wenn X Sauerstoff ist, R^4 nicht "geschütztes oder ungeschütztes Ureido(C_1-C_6)-alkyl" ist, und Salze davon, gekennzeichnet durch

(a) Reaktion einer Verbindung der Formel



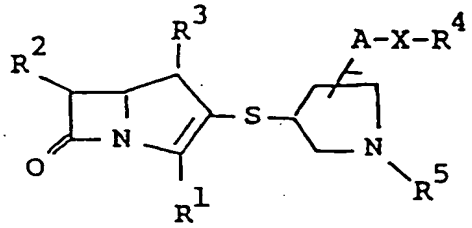
(II)

worin R^1, R^2 und R^3 jeweils wie oben definiert sind oder eines reaktionsfähigen Derivates an der Oxo-Gruppe davon oder Salze davon mit einer Verbindung der Formel



(III)

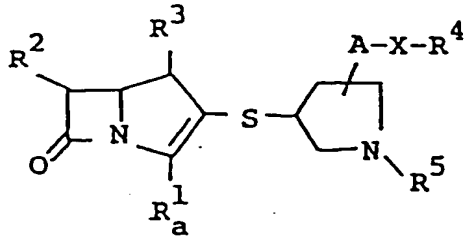
worin R^4, R^5, A und X jeweils wie oben definiert sind, oder Salze davon, um zu einer Verbindung der Formel



(I)

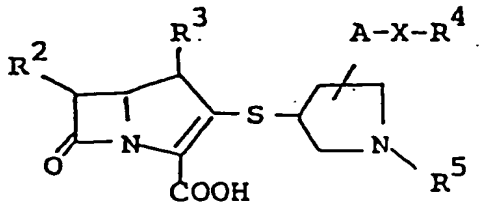
zu gelangen, worin R^1, R^2, R^3, R^4, R^5, A und X jeweils wie oben definiert sind, oder Salze davon; und

(b) Unterwerfen einer Verbindung der Formel



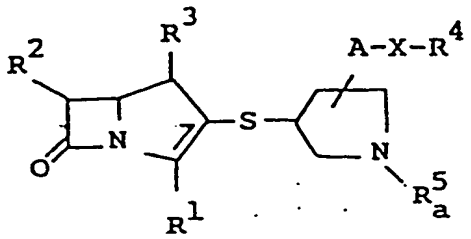
(Ia)

worin R^2, R^3, R^4, R^5, A und X jeweils wie oben definiert sind, und R^1_a geschütztes Carboxy darstellt, oder Salze davon, einer Eliminierungsreaktion der Carboxyschutzgruppe an R^1_a, um zu einer Verbinding der Formel



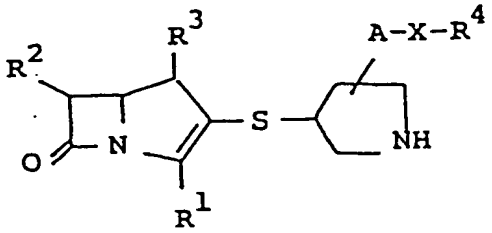
(Ib)

zu gelangen, worin R^2, R^3, R^4, R^5, A und X jeweils wie oben definiert sind, oder Salze davon; und
(c) Unterwerfen einer Verbindung der Formel



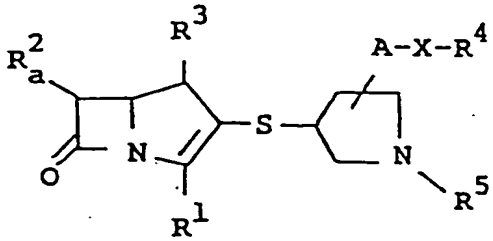
(Ic)

worin R^1, R^2, R^3, R^4, A und X jeweils wie oben definiert sind, und R^5_a ist eine Imino-Schutzgruppe, oder Salze davon, einer Eliminierungsreaktion der Imino-Schutzgruppe von R^5_a, um zu einer Verbindung der Formel



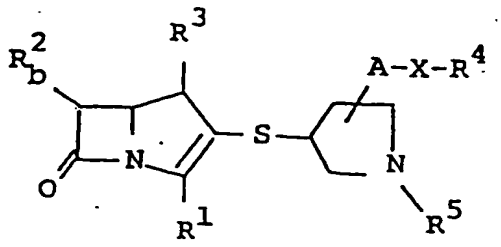
(Id)

zu gelangen, worin R^1, R^2, R^3, R^4, A und X jeweils wie oben definiert sind, oder Salzen davon; und
(d) Unterwerfen einer Verbindung der Formel



(Ie)

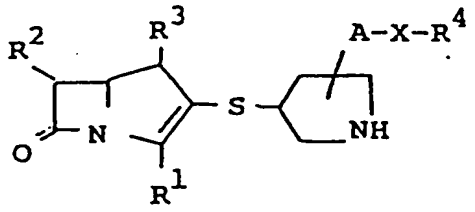
worin R^1, R^3, R^4, R^5, A und X jeweils wie oben definiert sind, und R^2_a ist geschütztes Hydroxy(C_1-C_6)-alkyl oder Salze davon, einer Eliminierungsreaktion der Hydroxy-Schutzgruppe an R^2_a, um zu einer Verbindung der Formel



(Ie)

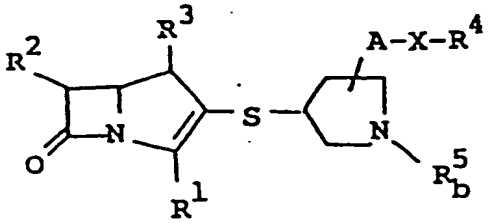
zu gelangen, worin R^1, R^3, R^4, R^5, A und X jeweils wie oben definiert sind und R^2_b ist Hydroxy(C_1-C_6)-alkyl, oder Salze davon; und

(e) Umsetzung einer Verbindung der Formel



(Id)

worin R^1, R^2, R^3, R^4, A und X jeweils wie oben definiert sind, oder Salze davon mit einem C_1-C_6-Alkanimidoylierungsmittel, um zu einer Verbindung der Formel



(Ig)

zu gelangen, worin R^1, R^2, R^3, R^4, A und X jeweils wie oben definiert sind, und R^5_b ist C_1-C_6-Alkanimidoyl, oder Salze davon.

2. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der Formel (I), worin
R^2 die Bedeutung Hydroxy(C_1-C_4)-alkyl hat,
R^3 ist Wasserstoff oder C_1-C_4-Alkyl,
R^4 ist Carbamoyloxy(C_1-C_4)-alkyl; [Phenyl(oder Nitrophenyl)-(C_1-C_4)-alkoxy]carbonyloxy(C_1-C_4)alkyl; [Triphenyl(C_1-C_4)-alkoxy](C_1-C_4)-alkyl; [Tri(C_1-C_4)-alkylsilyl]-oxy(C_1-C_4)-alkyl; Hydroxy(C_1-C_4)-alkyl; Hydroxy(C_1-C_4)-alkyl mit Amino- oder Phenyl- (oder Nitrophenyl-)(C_1-C_4)-alkoxycarbonylamino; Dihalo-(C_1-C_4)-alkyl; Carbamoyl(C_1-C_4)-alkyl; Trihalo(C_1-C_4)-alkanoylcarbamoyl(C_1-C_4)-alkyl; N-[Bis{(C_1-C_4)-alkoxyphenyl}(C_1-C_4)-alkyl]-carbamoyl(C_1-C_4)-alkyl; Halosulfonylcarbamoyl(C_1-C_4)-alkyl; Amino(C_1-C_4)-alkyl; N-[Phenyl-(oder Nitrophenyl-)(C_1-C_4)-alkoxycarbonyl]amino-(C_1-C_4)-alkyl; (C_1-C_4)-Alkylsulfonylamino-(C_1-C_4)-alkyl; Ureido(C_1-C_4)-alkyl; Phenyl(C_1-C_4)-alkylureido(C_1-C_4)-alkyl; Ureidocarbonyl(C_1-C_4)-alkyl, Phenyl(C_1-C_4)-alkylureidocarbonyl(C_1-C_4)-alkyl; Triazolyl(C_1-C_4)-alkyl; eine gesättigte oder ungesättigte 5- oder 6-gliedrige heteromonocyclische Gruppe, die 1 bis 4 Stickstoffatome enthält oder 1 bis 2 Schwefelatome und 1 bis 3 Stickstoffatome enthält, die C_1-C_4-Alkyl, N,N-Di(C_1-C_4)-alkylamino(C_1-C_4)-alkyl oder Phenyl- (oder Nitrophenyl-)(C_1-C_4)-alkoxycarbonyl oder (C_1-C_4)-Alkylsulfonyl, haben kann;
R^5 ist Wasserstoff oder C_1-C_6-Alkanimidoyl, und
A ist C_1-C_4-Alkylen.

3. Verfahren nach Anspruch 2, worin
R^3 die Bedeutung C_1-C_4-Alkyl hat, und
R^4 ist Carbamoyloxy(C_1-C_4)-alkyl; Hydroxy(C_1-C_4)-alkyl; Hydroxy(C_1-C_4)-alkyl, mit Amino oder Nitrophenyl(C_1-C_4)-alkoxycarbonylamino; Difluor(C_1-C_4)-alkyl; Carbamoyl(C_1-C_4)-alkyl; Amino(C_1-C_4)-alkyl; N-[Nitrophenyl(C_1-C_4)-alkoxycarbonylamino(C_1-C_4)-alkyl; (C_1-C_4)-Alkylsulfonylamino(C_1-C_4)-alkyl; Ureido(C_1-C_4)-alkyl; Ureidocarbonyl(C_1-C_4)-alkyl; Triazolyl(C_1-C_4)-alkyl; Tetrazolyl, Pyrrolidinyl, Thiadiazolyl oder Tetrazolyl, worin die genannten heterocyclischen Gruppen C_1-C_4-Alkyl, N,N-Di(C_1-C_4)-alkylamino-(C_1-C_4)-alkyl oder Nitrophenyl(C_1-C_4)-alkoxycarbonyl haben können; oder (C_1-C_4)-Alkylsulfonyl.

4. Verfahren nach Anspruch 3, worin
R^2 die Bedeutung 1-Hydroxyethyl hat,
R^3 ist Methyl,
R^4 ist 2-Hydroxyethyl, 2-Carbamoyloxyethyl, 3-Amino-2-hydroxypropyl, Difluormethyl, Carbamoylmethyl, 1-Carbamoyl-1-methylethyl, 2-Aminoethyl, 2-Amino-1,1-Dimethylethyl,2-(Methylsulfonylamino)-ethyl,2-Ureidoethyl,1,1-Dimethyl-2-ureidoethyl, Ureidocarbonylmethyl, 1,2,4-Triazolylmethyl, Pyrrolidinyl, Thiadiazolyl, 1-Methyl-1H-tetrazolyl, 1-[2-(N,N-Dimethylamino)ethyl]-1H-tetrazolyl oder Methylsulfonyl,
A ist Methylen, und
X ist Schwefel, Sauerstoff oder Imino.

5. Verfahren nach Anspruch 4 zur Herstellung der Verbindung (4R,5S,6S)-3-[(2S,4S)-2-{(2-Ureidoethyl)-thiomethyl}-pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-en-2-carbonsäure.

6. Verfahren nach Anspruch 4, worin R^4 die Bedeutung 2-Hydroxyethyl, 2-Carbamoyloxyethyl, Carbamoylmethyl, 1-Carbamoyl-1-methylethyl, 2-Aminoethyl oder 2-(Methylsulfonylamino)ethyl hat, und X ist Sauerstoff.

7. Verfahren nach Anspruch 6 zur Herstellung der Verbindung (4R,5S,6S)-3-[2S,4S)-(2-Aminoethyloxymethyl)-pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-en-2-carbonsäure-Acetat.

8. Verfahren nach Anspruch 4, worin R^4 die Bedeutung 2-Ureidoethyl oder Methylsulfonyl hat und X ist Imino.

9. Verfahren nach Anspruch 8 zur Herstellung der Verbindung (4R,5R,6S)-6-[(1R)-1-Hydroxyethyl]-4-methyl-7-oxo-3-[(2S,4S)-2-{2-ureidoethylaminomethyl}pyrrolidin-4-yl]thio-1-azabicyclo[3.2.0]hept-2-en-2-carbonsäure.

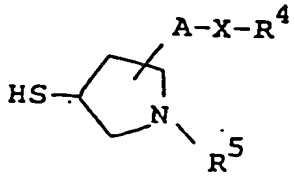
10. Verfahren nach Anspruch 2, worin R^3 Wasserstoff ist.

11. Verfahren nach Anspruch 10, worin R^4 eine ungesättigte 5- oder 6-gliedrige heteromonocyclische Gruppe ist, die 1 bis 4 Stickstoffstom(e) enthält.

12. Verfahren nach Anspruch 11, worin R^2 die Bedeutung 1-Hydroxyethyl hat, R^4 ist Pyridyl, R^5 ist Wasserstoff, A ist Methylen und X ist Schwefel.

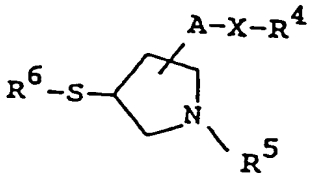
13. Verfahren nach Anspruch 12 zur Herstellung der Verbindung (5R,6S)-6-[(1R)-1-Hydroxyethyl]-7-oxo-3-[-(2S,4S)-2-(pyridin-4-yl)thiomethyl)pyrrolidin-4-ylthio]-1-azabicyclo[3.2.0.]hept-2-en-2-carbonsäure.

14. Verfahren zur Herstellung einer Verbindung der Formel



(III)

worin R^4, R^5, A und X jeweils wie oben definiert sind oder Salzen davon, dadurch gekennzeichnet, daß eine Verbindung der allgemeinen Formel

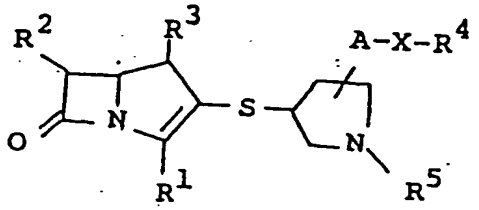


(IIIa)

worin R^4, R^5, A und X jeweils wie oben definiert sind und R^6 eine Mercapto-Schutzgruppe ist, oder Salze davon, einer Eliminierungsreaktion der Mercapto-Schutzgruppe von R^6 unterworfen wird.

Patentansprüche für folgenden Vertragsstaat : GR

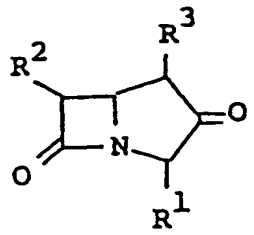
1. Verfahren zur Herstellung einer Verbindung der Formel



(I)

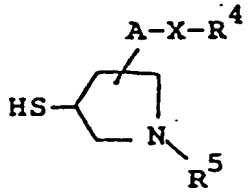
worin R^1 Carboxy oder geschütztes Carboxy darstellt, R^2 ist Hydroxy(C_1-C_4)-alkyl oder geschütztes Hydroxy(C_1-C_4)-alkyl, R^3 ist Wasserstoff oder C_1-C_6-Alkyl,
R^4 ist geschütztes oder ungeschütztes Hydroxy(C_1-C_4)-alkyl; geschütztes oder ungeschütztes Hydroxy-(C_1-C_4)-alkyl mit geschütztem oder ungeschütztem Amino; Halo(C_1-C_6)-alkyl; geschütztes oder ungeschütztes Carbamoyl(C_1-C_6)-alkyl; geschütztes oder ungeschütztes Amino(C_1-C_6)-alkyl; geschütztes oder ungeschütztes Ureido(C_1-C_6)-alkyl; geschütztes oder ungeschütztes Ureidocarbonyl(C_1-C_6)-alkyl; Triazolyl(C_1-C_6)-alkyl; eine gesättigte oder ungesättigte 5- oder 6-gliedrige heteromonocyclische Gruppe, die 1 bis 4 Stickstoffatome enthält oder 1 bis 2 Schwefelatome und 1 bis 3 Stickstoffatome, worin die genannte heterocyclische Gruppe substituiert sein kann durch geeignete Substituenten, ausgewählt unter (C_1-C_6)-Alkyl, Amino, Amino(C_1-C_6)-alkyl; Mono-(oder Di-)(C_1-C_6)-alkylamino, Mono-(oder Di)(C_1-C_6)-alkylamino(C_1-C_6)-alkyl und die Imino-Schutzgruppe; oder C_1-C_6-Alkylsulfonyl;
R^5 ist Wasserstoff, C_1-C_6-Alkanimidoyl oder Imino-Schutzgruppe,
A ist C_1-C_4-Alkylen, und
X ist Schwefel, Sauerstoff, Imino oder geschütztes Imino, vorausgesetzt, daß wenn X Sauerstoff ist, R^4 nicht "geschütztes oder ungeschütztes Ureido(C_1-C_6)-alkyl" ist, und Salze davon, gekennzeichnet durch

(a) Reaktion einer Verbindung der Formel



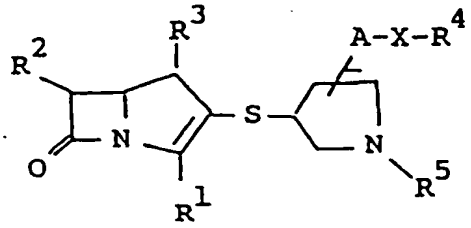
(II)

worin R^1, R^2 und R^3 jeweils wie oben definiert sind oder eines reaktionsfähigen Derivates an der Oxo-Gruppe davon oder Salze davon mit einer Verbindung der Formel



(III)

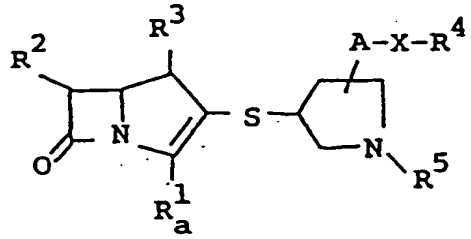
worin R^4, R^5, A und X jeweils wie oben definiert sind, oder Salze davon, um zu einer Verbindung der Formel



(I)

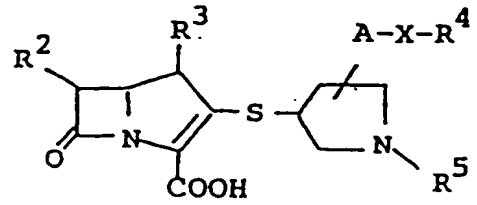
zu gelangen, worin R^1, R^2, R^3, R^4, R^5, A und X jeweils wie oben definiert sind, oder Salze davon; und

(b) Unterwerfen einer Verbindung der Formel



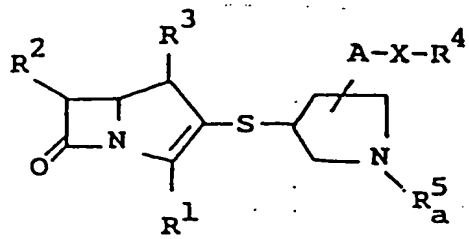
(Ia)

worin R^2, R^3, R^4, R^5, A und X jeweils wie oben definiert sind, und R_a^1 geschütztes Carboxy darstellt, oder Salze davon, einer Eliminierungsreaktion der Carboxyschutzgruppe an R_a^1, um zu einer Verbindung der Formel



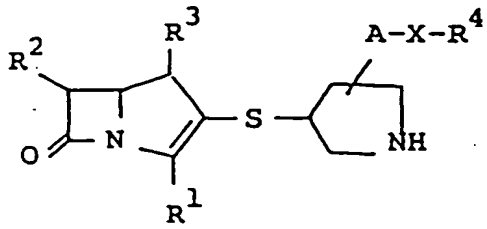
(Ib)

zu gelangen, worin R^2, R^3, R^4, R^5, A und X jeweils wie oben definiert sind, oder Salze davon; und
(c) Unterwerfen einer Verbindung der Formel



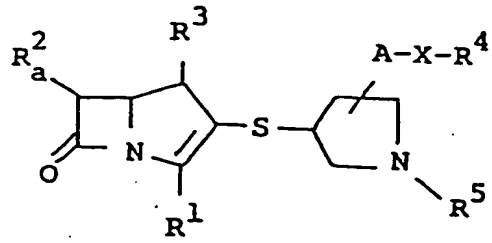
(Ic)

worin R^1, R^2, R^3, R^4, A und X jeweils wie oben definiert sind, und R^5_a ist eine Imino-Schutzgruppe, oder Salze davon, einer Eliminierungsreaktion der Imino-Schutzgruppe von R^5_a, um zu einer Verbindung der Formel



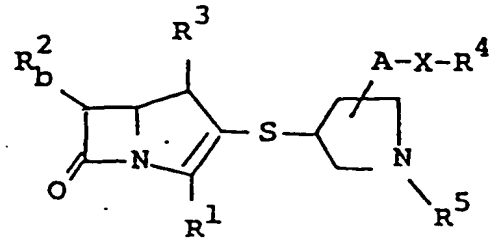
(Id)

zu gelangen, worin R^1, R^2, R^3, R^4, A und X jeweils wie oben definiert sind, oder Salzen davon; und
(d) Unterwerfen einer Verbindung der Formel



(Ie)

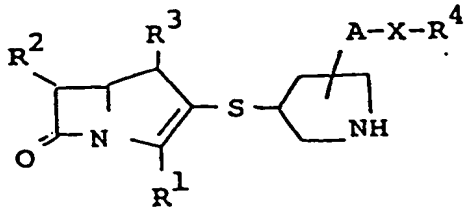
worin R^1, R^3, R^4, R^5, A und X jeweils wie oben definiert sind, und R^2_a ist geschütztes Hydroxy(C_1-C_6)-alkyl oder Salze davon, einer Eliminierungsreaktion der Hydroxy-Schutzgruppe an R^2_a, um zu einer Verbindung der Formel



(Ie)

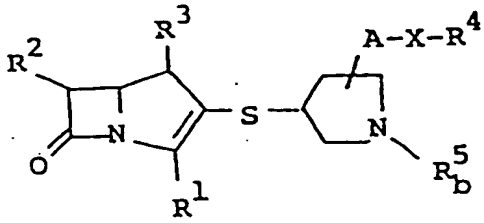
zu gelangen, worin R^1, R^3, R^4, R^5, A und X jeweils wie oben definiert sind und R_b^2 ist Hydroxy(C_1-C_6)-alkyl, oder Salze davon; und

(e) Umsetzung einer Verbindung der Formel



(Id)

worin R^1, R^2, R^3, R^4, A und X jeweils wie oben definiert sind, oder Salze davon mit einem C_1-C_6-Alkanimidoylierungsmittel, um zu einer Verbindung der Formel



(Ig)

zu gelangen, worin R^1, R^2, R^3, R^4, A und X jeweils wie oben definiert sind, und R_b^5 ist C_1-C_6-Alkanimidoyl, oder Salze davon.

2. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der Formel (I), worin
R^2 die Bedeutung Hydroxy(C_1-C_4)-alkyl hat,
R^3 ist Wasserstoff oder C_1-C_4-Alkyl,
R^4 ist Carbamoyloxy(C_1-C_4)-alkyl; [Phenyl(oder Nitrophenyl)-(C_1-C_4)-alkoxy]carbonyloxy(C_1-C_4)-alkyl; [Triphenyl(C_1-C_4)alkoxy](C_1-C_4)-alkyl; [Tri(C_1-C_4)-alkylsilyl]-oxy(C_1-C_4)-alkyl; Hydroxy(C_1-C_4)-alkyl; Hydroxy(C_1-C_4)-alkyl mit Amino- oder Phenyl- (oder Nitrophenyl-)(C_1-C_4)-alkoxycarbonylamino; Dihalo-(C_1-C_4)-alkyl; Carbamoyl(C_1-C_4)-alkyl; Trihalo(C_1-C_4)-alkanoylcarbamoyl(C_1-C_4)-alkyl; N-[Bis{(C_1-C_4)-alkoxyphenyl}(C_1-C_4)-alkyl]-carbamoyl(C_1-C_4)-alkyl; Halosulfonylcarbamoyl(C_1-C_4)-alkyl; Amino(C_1-C_4)-alkyl; N-[Phenyl(oder Nitrophenyl-)(C_1-C_4)-alkoxycarbonyl]amino-(C_1-C_4)-alkyl; (C_1-C_4)-Alkylsulfonylamino-(C_1-C_4)-alkyl; Ureido(C_1-C_4)-alkyl; Phenyl(C_1-C_4)-alkylureido(C_1-C_4)-alkyl; Ureidocarbonyl(C_1-C_4)-alkyl; Phenyl(C_1-C_4)-alkylureidocarbonyl(C_1-C_4)-alkyl; Triazolyl(C_1-C_4)-alkyl; eine gesättigte oder ungesättigte 5- oder 6-gliedrige heteromonocyclische Gruppe, die 1 bis 4 Stickstoffatome enthält oder 1 bis 2 Schwefelatome und 1 bis 3 Stickstoffatome enthält, die C_1-C_4-Alkyl, N,N-Di(C_1-C_4)-alkylamino(C_1-C_4)-alkyl oder Phenyl- (oder Nitrophenyl-)(C_1-C_4)-alkoxycarbonyl oder (C_1-C_4)-Alkylsulfonyl, haben kann;
R^5 ist Wasserstoff oder C_1-C_6-Alkanimidoyl, und
A ist C_1-C_4-Alkylen.

3. Verfahren nach Anspruch 2, worin
R^3 die Bedeutung C_1-C_4-Alkyl hat, und
R^1 ist Carbamoyloxy(C_1-C_4)-alkyl; Hydroxy(C_1-C_4)-alkyl; Hydroxy(C_1-C_4)-alkyl mit Amino oder Nitrophenyl(C_1-C_4)-alkoxycarbonylamino; Difluor(C_1-C_4)-alkyl; Carbamoyl(C_1-C_4)-alkyl; Amino(C_1-C_4)-alkyl; N-[Nitrophenyl(C_1-C_4)-alkoxycarbonylamino(C_1-C_4)-alkyl; (C_1-C_4)-Alkylsulfonylamino(C_1-C_4)-alkyl; Ureido(C_1-C_4)-alkyl; Ureidocarbonyl(C_1-C_4)-alkyl; Triazolyl(C_1-C_4)-alkyl; Tetrazolyl, Pyrrolidinyl, Thiadiazolyl oder Tetrazolyl, worin die genannten heterocyclischen Gruppen C_1-C_4-Alkyl, N,N-Di(C_1-C_4)-alkylamino-(C_1-C_4)-alkyl oder Nitrophenyl(C_1-C_4)-alkoxycarbonyl haben können; oder (C_1-C_4)-Alkylsulfonyl.

4. Verfahren nach Anspruch 3, worin
R^2 die Bedeutung 1-Hydroxyethyl hat,
R^3 ist Methyl,
R^4 ist 2-Hydroxyethyl, 2-Carbamoyloxyethyl, 3-Amino-2-hydroxypropyl, Difluormethyl, Carbamoylmethyl, 1-Carbamoyl-1-methylethyl, 2-Aminoethyl, 2-Amino-1,1-Dimethylethyl,2-(Methylsulfonylamino)-ethyl,2-Ureidoethyl,1,1-Dimethyl-2-ureidoethyl, Ureidocarbonylmethyl, 1,2,4-Triazolylmethyl, Pyrrolidinyl, Thiadiazolyl, 1-Methyl-1H-tetrazolyl, 1-[2-(N,N-Dimethylamino)ethyl]-1H-tetrazolyl oder Methylsulfonyl,
A ist Methylen, und
X ist Schwefel, Sauerstoff oder Imino.

5. Verfahren nach Anspruch 4 zur Herstellung der Verbindung (4R,5S,6S)-3-[(2S,4S)-2-{(2-Ureidoethyl)-thiomethyl}-pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-en-2-carbonsäure.

6. Verfahren nach Anspruch 4, worin R^4 die Bedeutung 2-Hydroxyethyl, 2-Carbamoyloxyethyl, Carbamoylmethyl, 1-Carbamoyl-1-methylethyl, 2-Aminoethyl oder 2-(Methylsulfonylamino)ethyl hat, und X ist Sauerstoff.

7. Verfahren nach Anspruch 6 zur Herstellung der Verbindung (4R,5S,6S)-3-[2S,4S)-(2-Aminoethyloxymethyl)-pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-en-2-carbonsäure-Acetat.

8. Verfahren nach Anspruch 4, worin R^4 die Bedeutung 2-Ureidoethyl oder Methylsulfonyl hat und X ist Imino.

9. Verfahren nach Anspruch 8 zur Herstellung der Verbindung (4R,5R,6S)-6-[(1R)-1-Hydroxyethyl]-4-methyl-7-oxo-3-[(2S,4S)-2-{2-ureidoethylaminomethyl}pyrrolidin-4-yl]thio-1-azabicyclo[3.2.0]hept-2-en-2-carbonsäure.

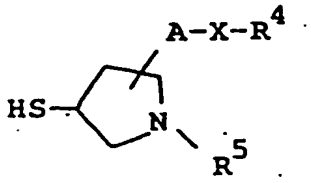
10. Verfahren nach Anspruch 2, worin R^3 Wasserstoff ist.

11. Verfahren nach Anspruch 10, worin R^4 eine ungesättigte 5- oder 6-gliedrige heteromonocyclische Gruppe ist, die 1 bis 4 Stickstoffatom(e) enthält.

12. Verfahren nach Anspruch 11, worin R^2 die Bedeutung 1-Hydroxyethyl hat, R^4 ist Pyridyl, R^5 ist Wasserstoff, A ist Methylen und X ist Schwefel.

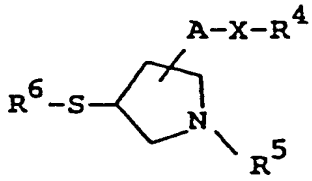
13. Verfahren nach Anspruch 12 zur Herstellung der Verbindung (5R,6S)-6-[(1R)-1-Hydroxyethyl]-7-oxo-3-[-(2S,4S)-2-(pyridin-4-ylthiomethyl)pyrrolidin-4-ylthio]-1-azabicyclo[3.2.0.]hept-2-en-2-carbonsäure.

14. Verfahren zur Herstellung einer Verbindung der Formel



(III)

worin R^4, R^5, A und X jeweils wie oben definiert sind oder Salzen davon, dadurch gekennzeichnet, daß eine Verbindung der allgemeinen Formel



(IIIa)

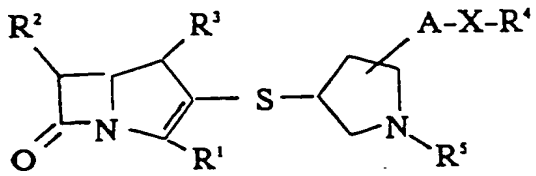
worin R^4, R^5, A und X jeweils wie oben definiert sind und R^6 eine Mercapto-Schutzgruppe ist, oder Salze davon, einer Eliminierungsreaktion der Mercapto-Schutzgruppe von R^6 unterworfen wird.

15. Modifizierung des Verfahrens nach einem der Ansprüche 1 bis 13, dadurch gekennzeichnet, daß eine nach einem Verfahren gemäß einem der Ansprüche 1 bis 13 hergestellte Verbindung in eine pharmazeutisch annehmbare Form gebracht wird durch Vermischen oder Präsentation der Verbindung mit einem pharmazeutisch annehmbaren Träger oder Exzipienten.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Composé de la formule :



(I)

dans laquelle
R^1 est un carboxy ou un carboxy protégé,
R^2 est un hydroxy(C_1-C_4)alkyle ou un hydroxy(C_1-C_4)alkyle protégé,
R^3 est un hydrogène ou un (C_1-C_6)alkyle,
R^4 est un hydroxy(C_1-C_6)alkyle protégé ou non protégé; un hydroxy(C_1-C_6)alkyle protégé ou non protégé ayant un amino protégé ou non protégé; un halo(C_1-C_6)alkyle; un carbamoyl(C_1-C_6)alkyle protégé ou non protégé; un amino (C_1-C_6)alkyle protégé ou non protégé; un uréido(C_1-C_6)alkyle protégé ou non protégé; un uréiodocarbonyl(C_1-C_6)alkyle protégé ou non protégé; un triazolyl(C_1-C_6)alkyle; un groupe hétéromonocyclique saturé ou insaturé à 5 ou 6 éléments contenant 1 à 4 atomes d'azote ou contenant 1 à 2 atomes de soufre et 1 à 3 atomes d'azote, où ledit groupe hétérocyclique peut être substitué par un ou des substituants appropriés choisis parmi (C_1-C_6)alkyl, amino, amino(C_1-C_6)alkyle, mono- (ou di-) (C_1-C_6)alkylamino, mono- (ou di-) (C_1-C_6)alkylamino(C_1-C_6)alkyle et groupe imino-protecteur; ou un (C_1-C_6)alkylsulfonyle;
R^5 est un hydrogène, un (C_1-C_6)alcaneimidoyle ou un groupe imino-protecteur,

A est un (C_1-C_4)alcylène et
X est un soufre, un oxygène, un imino ou un imino protégé,
à condition que
lorsque X st un oxygène,
alors R^4 est un "uréido(C_1-C_6)alkyle protégé ou non protégé",
et les sels de celui-ci acceptables sur le plan pharmaceutique.

2. Composé selon la revendication 1, dans lequel
R^2 est un hydroxy(C_1-C_4)alkyle,
R^3 est un hydrogène ou un (C_1-C_4)alkyle,
R^4 est un carbamoyloxy(C_1-C_4)alkyle; un [phényl- (ou nitrophényl-) (C_1-C_4)alcoxy]carbonyloxy(C_1-C_4)-alkyle; un [triphényl(C_1-C_4)alcoxy](C_1-C_4)alkyle; un [tri(C_1-C_4)alkylsilyl]oxy(C_1-C_4)alkyle; un hydroxy(C_1-C_4)alkyle; un hydroxy(C_1-C_4)alkyle ayant un amino ou un phényl- (ou nitrophényl-) (C_1-C_4)-alcoxycarbonylamino; un dihalo(C_1-C_4)alkyle; un carbamoyl(C_1-C_4)alkyle; un trihalo(C_1-C_4)-alcanoylcarbamoyl(C_1-C_4)alkyle; un N-[bis{(C_1-C_4)alcoxyphényl}(C_1-C_4)alkyl]carbamoyl(C_1-C_4)alkyle; un halosulfonylcarbamoyl(C_1-C_4)alkyle; un amino(C_1-C_4)alkyle; un N-[phényl (ou nitrophényl-)(C_1-C_4)-alcoxycarbonyl]amino(C_1-C_4)alkyle; un (C_1-C_4)alkylsulfonylamino(C_1-C_4)alkyle; un uréido(C_1-C_4)alkyle; un phényl(C_1-C_4)alkyluréido(C_1-C_4)alkyle; un uréidocarbonyl(C_1-C_4)alkyle; un phényl(C_1-C_4)-alkyluréidocarbonyl(C_1-C_4)alkyle; un triazolyl(C_1-C_4)alkyle; un groupe hétéromonocyclique saturé ou insaturé à 5 ou 6 éléments contenant 1 à 4 atomes d'azote ou contenant 1 à 2 atomes de soufre et 1 à 3 atomes d'azote, qui peut avoir un (C_1-C_4)alkyle, un N,N-di(C_1-C_4)alkylamino(C_1-C_4)alkyle ou un phényl- (ou un nitrophényl-) (C_1-C_4)alcoxycarbonyle; ou un (C_1-C_4)alkylsulfonyle;
R^5 est un hydrogène ou un (C_1-C_4)alcaneimidoyle, et
A est un (C_1-C_4)alcylène.

3. Composé selon la revendication 2, dans lequel
R^3 est un (C_1-C_4)alkyle et
R^4 est un carbamoyloxy(C_1-C_4)alkyle; un hydroxy(C_1-C_4)alkyle; un hydroxy(C_1-C_4)alkyle ayant un amino ou un nitrophényl(C_1-C_4)-alcoxycarbonylamino; un difluoro(C_1-C_4)alkyle; un carbamoyl(C_1-C_4)-alkyle; un amino(C_1-C_4)alkyle; un N-[nitrophényl(C_1-C_4)alcoxycarbonylamino(C_1-C_4)alkyle; un (C_1-C_4)-alkylsulfonylamino(C_1-C_4)alkyle; un uréido(C_1-C_4)alkyle; un uréidocarbonyl(C_1-C_4)alkyle; un triazolyl(C_1-C_4)alkyle; un tétrazolyle, un pyrrolidinyle, un thiadiazolyle ou un tétrazolyle, où lesdits groupes hétérocycliques peuvent avoir un (C_1-C_4)alkyle, un N,N-di(C_1-C_4)alkylamino(C_1-C_4)alkyle ou un nitrophényl(C_1-C_4)alcoxycarbonyle; ou un (C_1-C_4)alkylsulfonyle.

4. Composé selon la revendication 3, dans lequel
R^2un hydroxyéthyle,
R^3est un méthyle,
R^4 est un 2-hydroxyéthyle, un 2-carbamoyloxyéthyle, un 3-amino-2-hydroxypropyle, un difluorométhyle, un carbamoylméthyle, un 1-carbamoyl-1-méthyléthyle, un 2-aminoéthyle, un 2-amino-1,1-diméthyléthyle, un 2-(méthylsulfonylamino)éthyle, un 2-uréidoéthyle, un 1,1-diméthyl-2-uréidoéthyle, un uréidocarbonylméthyle, un 1,2,4-triazolylméthyle, un pyrrolidinyle, un thiadiazolyle, un 1-méthyl-1H-tétrazolyle, un 1-[2-(N,N-diméthylamino)éthyl]-1H-tétrazolyle, ou un méthylsulfonyle,
A est un méthylène, et
X est un soufre, un oxygène ou un imino.

5. Composé selon la revendication 4, qui est l'acide (4R,5S,6S)-3-[(2S,4S)-2-{(2-uréidoéthyl)-thiométhyl}pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyéthyl]-4-méthyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ène-2-carboxylique.

6. Composé selon la revendication 4, dans lequel
R^4 est un 2-hydroxyéthyle, un 2-carbamoyloxyéthyle, un carbamoylméthyle, un 1-carbamoyl-1-méthyléthyle, un 2-aminoéthyle ou un 2-(méthylsulfonylamino)éthyle et
X est un oxygène.

7. Composé selon la revendication 6, qui est l'acétate de l'acide (4R,5S,6S)-3-[(2S,4S)-2-(2-aminoéthyloxyméthyl)pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyéthyl]4-méthyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ène-2-carboxylique.

8. Composé selon la revendication 4, dans lequel
R^4 est un 2-uréidoéthyle ou un méthylsulfonyle et
X est un imino.

9. Composé selon la revendication 8, qui est l'acide (4R,5S,6S)-6-[(1R)-1-hydroxyéthyl]-4-méthyl-7-oxo-3-[(2S,4S)-2-{(2-uréidoéthyl)aminométhyl}pyrrolidin-4-yl]thio-1-azabicyclo[3.2.0]hept-2-ène-2-carboxylique.

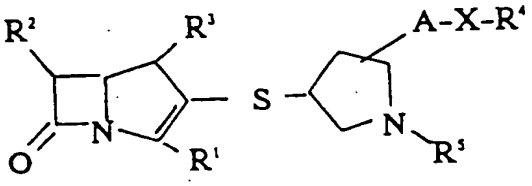
10. Composé selon la revendication 2, dans lequel
R^3 est un hydrogène.

11. Composé selon la revendication 10, dans lequel
R^4 est un groupe hétéromonocyclique insaturé à 5 ou 6 éléments contenant de 1 à 4 atomes d'azote.

12. Composé selon la revendication 11, dans lequel
R^2 est un 1-hydroxyéthyle,
R^4 est un pyridyle,
R^5 est un hydrogène,
A est un méthylène, et
X est un soufre.

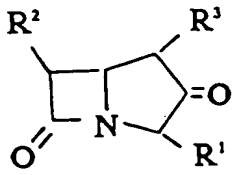
13. Composé selon la revendication 12, qui est l'acide (5R,6S)-6-[(1R)-1-hydroxyéthyl]-7-oxo-3-[(2S,4S)-2-(pyridin-4-ylthiométhyl)pyrrolidin-4-yl-thio]-1-azabicyclo[3.2.0]hept-2-ène-2-carboxylique.

14. Procédé pour la préparation d'un composé de la formule :



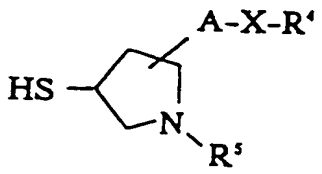
(I)

dans laquelle R^1 à R^5, A et X sont définis comme dans la revendication 1 et les sels de celui-ci, qui comprend de :
(a) faire réagir un composé de la formule



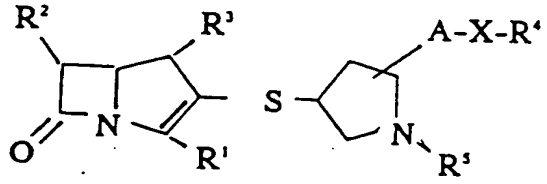
(II)

dans laquelle R^1, R^2 et R^3 sont chacun comme défini ci-dessus, ou un dérivé réactif de celui-ci au groupe oxo, ou les sels celui-ci, avec un composé de la formule :



(III)

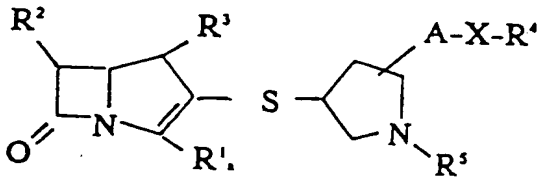
dans laquelle R^4, R^5, A et X sont chacun comme défini ci-dessus ou les sels de celui-ci, pour donner un composé de la formule :



(I)

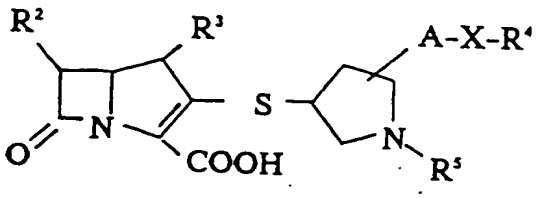
dans laquelle R^1, R^2, R^3, R^4, R^5, A et X sont chacun comme défini ci-dessus, ou les sels de celui-ci; et de

(b) soumettre un composé de la formule :



(Ia)

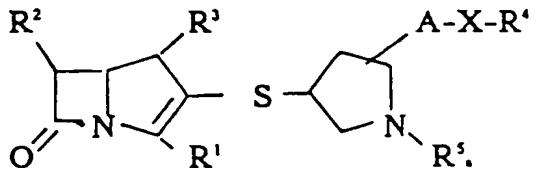
dans laquelle R^2, R^3, R^4, R^5, A et X sont chacun comme défini ci-dessus, et R_a^1 est un carboxy protégé, ou les sels de celui-ci, à une réaction d'élimination du groupe carboxy-protecteur sur R_a^1 pour donner un composé de la formule :



(Ib)

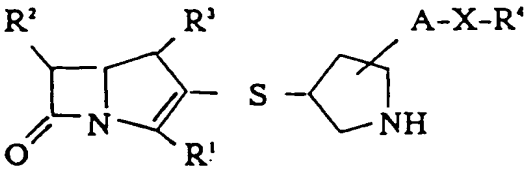
dans laquelle R^2, R^3, R^4, R^5, A et X sont chacun comme défini ci-dessus, ou les sels de celui-ci; et

(c) de soumettre un composé de la formule :



(Ic)

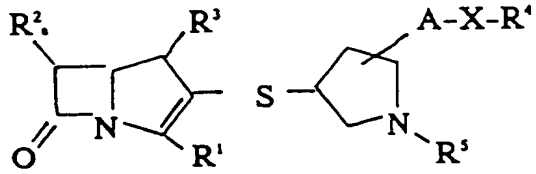
dans laquelle R^1, R^2, R^3, R^4, A et X sont chacun comme défini ci-dessus, et R_a^5 est un groupe imino-protecteur, ou les sels de celui-ci, à une réaction d'élimination du groupe imino-protecteur de R_a^5 pour donner un composé de la formule :



(Id)

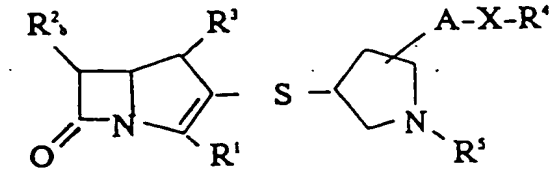
dans laquelle R^1, R^2, R^3, R^4, A et X sont chacun comme défini ci-dessus, ou les sels de celui-ci; et de

(d) soumettre un composé de la formule :



(Ie)

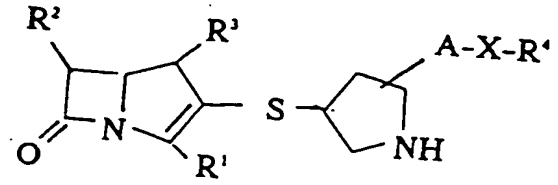
dans laquelle R^1, R^3, R^4, R^5, A et X sont chacun comme défini ci-dessus, et R_a^2 est un groupe hydroxy(C_1-C_6)alkyle protégé, ou les sels de celui-ci, à une réaction d'élimination du groupe hydroxy-protecteur sur R_a^2 pour donner un composé de la formule :



(If)

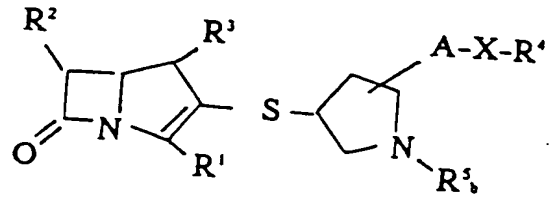
dans laquelle R^1, R^3, R^4, R^5, A et X sont chacun comme défini ci-dessus et R_b^2 est un hydroxy(C_1-C_6)alkyle, ou les sels de celui-ci; et de

(e) faire réagir un composé de la formule :



(Id)

dans laquelle R^1, R^2, R^3, R^4, A et X sont chacun comme défini ci-dessus ou les sels de celui-c avec un agent de (C_1-C_6)alcaneimidoylation pour donner un composé de la formule :



(Ig)

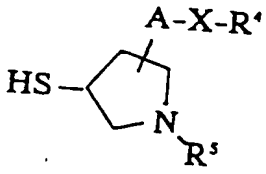
dans laquelle R^1, R^2, R^3, R^4, A et X sont chacun comme défini ci-dessus et R^5_b est un (C_1-C_6)-alcaneimidoyle ou les sels de celui-ci.

15. Composition pharmaceutique comprenant comme ingrédient actif, un composé de la revendication 1, en mélange avec un vecteur ou un excipient acceptable sur le plan pharmaceutique.

16. Composé de la revendication 1, pour une utilisation comme médicament.

17. Composé de la revendication 1, pour le traitement de maladies infectieuses.

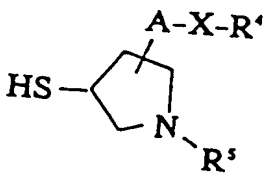
18. Composé de la formule :



(III)

dans laquelle R^4, R^5, A et X sont chacun comme défini ci-dessus ou les sels de celui-ci.

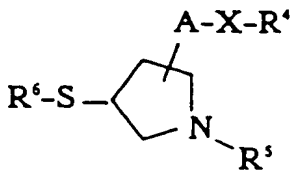
19. Procédé pour la préparation d'un composé de la formule :



(III)

dans laquelle R^4, R^5, A et X sont chacun comme défini ci-dessus ou les sels de celui-ci, qui comprend

de soumettre un composé de la formule :

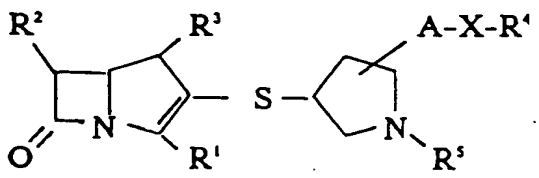


(IIIa)

dans laquelle R^4, R^5, A et X sont chacun comme défini ci-dessus et R^6 est un groupe mercapto-protecteur, ou les sels de celui-ci, à une réaction d'élimination du groupe mercapto-protecteur R^6.

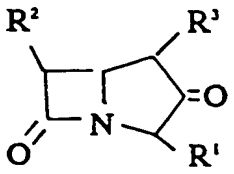
Revendications pour l'Etat contractant suivant : ES

1. Procédé pour préparer un composé de la formule :

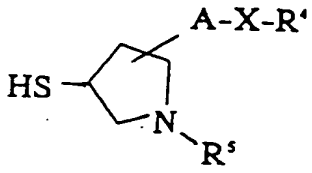


(I)

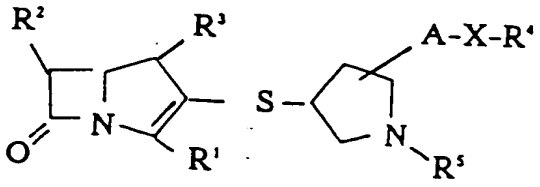
dans laquelle
R^1 est un carboxy ou un carboxy protégé,
R^2 est un hydroxy(C_1-C_4)alkyle ou un hydroxy(C_1-C_4)alkyle protégé,
R^3 est un hydrogène ou un (C_1-C_6)alkyle,
R^4 est un hydroxy(C_1-C_6)alkyle protégé ou non protégé; un hydroxy(C_1-C_6)alkyle protégé ou non protégé ayant un amino protégé ou non protégé; un halo(C_1-C_6)alkyle; un carbamoyl(C_1-C_6)alkyle protégé ou non protégé; un amino (C_1-C_6)alkyle protégé ou non protégé; un uréido(C_1-C_6)alkyle protégé ou non protégé; un uréiodocarbonyl(C_1-C_6)alkyle protégé ou non protégé; un triazolyl(C_1-C_6)-alkyle; un groupe hétéromonocyclique saturé ou insaturé à 5 ou 6 éléments contenant 1 à 4 atomes d'azote ou contenant 1 à 2 atomes de soufre et 1 à 3 atomes d'azote, où ledit groupe hétérocyclique peut être substitué par un ou des substituants appropriés choisis parmi (C_1-C_6)alkyl, amino, amino(C_1-C_6)alkyle, mono- (ou di-) (C_1-C_6)alkylamino, mono- (ou di-) (C_1-C_6)alkylamino(C_1-C_6)alkyle et groupe imino-protecteur; ou un (C_1-C_6)alkylsulfonyle;
R^5 est un hydrogène, un (C_1-C_6)alcaneimidoyle ou un groupe imino-protecteur,
A est un (C_1-C_4)alcylène et
X est un soufre, un oxygène, un imino ou un imino protégé,
à condition que
lorsque X est un oxygène,
alors R^4 est un "uréido(C_1-C_6)alkyle protégé ou non protégé",
et les sels de celui-ci, qui comprend de :
(a) faire réagir un composé de la formule



dans laquelle R^1, R^2 et R^3 sont chacun comme défini ci-dessus, ou un dérivé réactif de celui-ci au group oxo, ou les sels celui-ci, avec un composé de la formule :

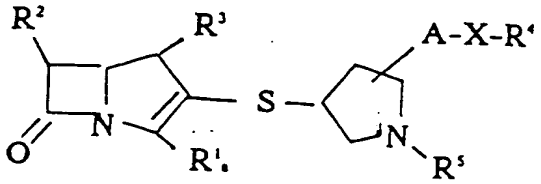


dans laquelle R^4, R^5, A et X sont chacun comme défini ci-dessus ou les sels de celui-ci, pour donner un composé de la formule :

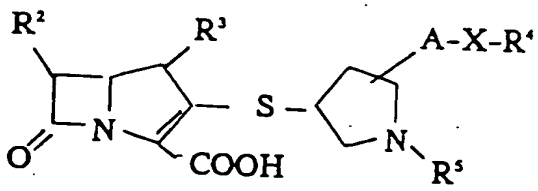


dans laquelle R^1, R^2, R^3, R^4, R^5, A et X sont chacun comme défini ci-dessus, ou les sels de celui-ci; et de

(b) soumettre un composé de la formule :

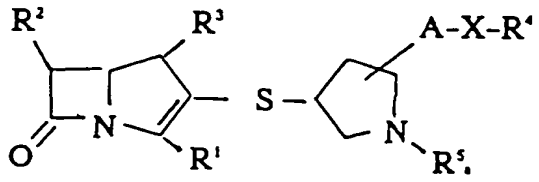


dans laquelle R^2, R^3, R^4, R^5, A et X sont chacun comme défini ci-dessus, et R_a^1 est un carboxy protégé, ou les sels de celui-ci, à une réaction d'élimination du groupe carboxy-protecteur sur R_a^1 pour donner un composé de la formule :

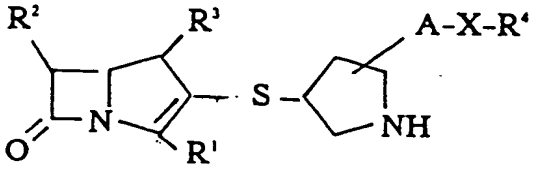


dans laquelle R^2, R^3, R^4, R^5, A et X sont chacun comme défini ci-dessus, ou les sels de celui-ci; et

(c) de soumettre un composé de la formule :

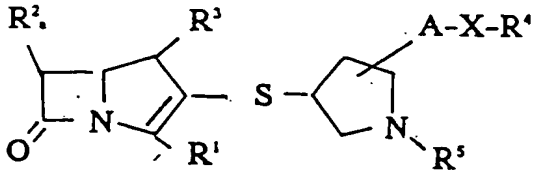


dans laquelle R^1, R^2, R^3, R^4, A et X sont chacun comme défini ci-dessus, et R^5_a est un groupe imino-protecteur, ou les sels de celui-ci, à une réaction d'élimination du groupe imino-protecteur de R^5_a pour donner un composé de la formule :

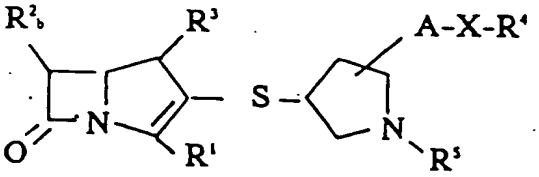


dans laquelle R^1, R^2, R^3, R^4, A et X sont chacun comme défini ci-dessus, ou les sels de celui-ci; et de

(d) soumettre un composé de la formule :

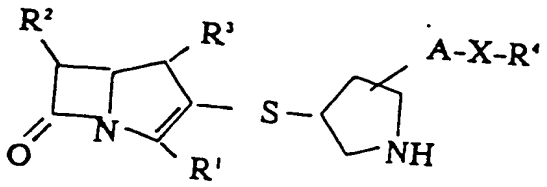


dans laquelle R^1, R^3, R^4, R^5, A et X sont chacun comme défini ci-dessus, et R^2_a est un groupe hydroxy(C_1-C_6)alkyle protégé, ou les sels de celui-ci, à une réaction d'élimination du groupe hydroxy-protecteur sur R^2_a pour donner un composé de la formule :

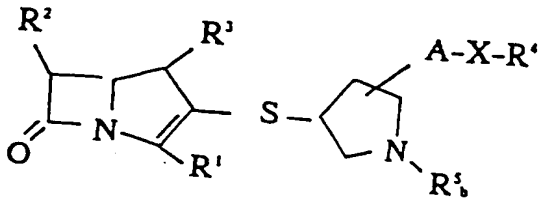


dans laquelle R^1, R^3, R^4, R^5, A et X sont chacun comme défini ci-dessus et R^2_b est un hydroxy(C_1-C_6)alkyle, ou les sels de celui-ci; et de

(e) faire réagir un composé de la formule :



dans laquelle R^1, R^2, R^3, R^4, A et X sont chacun comme défini ci-dessus ou les sels de celui-ci avec un agent de (C_1-C_6)alcaneimidoylation pour donner un composé de la formule :



dans laquelle R^1, R^2, R^3, R^4, A et X sont chacun comme défini ci-dessus et R^5_b est un (C_1-C_6)-alcaneimidoyle ou les sels de celui-ci.

2. Procédé selon la revendication 1 pour préparer un composé de la formule (i) dans laquelle :
R^2 est un hydroxy(C_1-C_4)alkyle,
R^3 est un hydrogène ou un (C_1-C_4)alkyle,
R^4 est un carbamoyloxy(C_1-C_4)alkyle; un [phényl- (ou nitrophényl-) (C_1-C_4)alcoxy]carbonyloxy(C_1-C_4)-alkyle; un [triphényl(C_1-C_4)alcoxy](C_1-C_4)alkyle; un [tri(C_1-C_4)alkylsilyl]oxy(C_1-C_4)alkyle; un hydroxy(C_1-C_4)alkyle ayant un amino ou un phényl- (ou nitrophényl-)(C_1-C_4)-alcoxycarbonylamino; un dihalo(C_1-C_4)alkyle; un carbamoyl(C_1-C_4)alkyle; un trihalo(C_1-C_4)-alcanoylcarbamoyl(C_1-C_4)alkyle; un N-[bis{(C_1-C_4)alcoxyphényl}(C_1-C_4)alkyl]carbamoyl(C_1-C_4)alkyle; un halosulfonylcarbamoyl(C_1-C_4)alkyle; un amino(C_1-C_4)alkyle; un N-[phényl (ou nitrophényl-)(C_1-C_4)-alcoxycarbonyl]amino(C_1-C_4)alkyle; un (C_1-C_4)alkylsulfonylamino(C_1-C_4)alkyle; un uréido(C_1-C_4)alkyle; un phényl(C_1-C_4)alkyluréido(C_1-C_4)alkyle; un uréidocarbonyl(C_1-C_4)alkyle; un phényl(C_1-C_4)-alkyluréidocarbonyl(C_1-C_4)alkyle; un triazolyl(C_1-C_4)alkyle; un groupe hétéromonocyclique saturé ou insaturé à 5 ou 6 éléments contenant 1 à 4 atomes d'azote ou contenant 1 à 2 atomes de soufre et 1 à 3 atomes d'azote, qui peut avoir un (C_1-C_4)alkyle, un N,N-di(C_1-C_4)alkylamino(C_1-C_4)alkyle ou un phényl- (ou un nitrophényl-) (C_1-C_4)alcoxycarbonyle; ou un (C_1-C_4)alkylsulfonyle;
R^5 est un hydrogène ou un (C_1-C_4)alcaneimidoyle, et
A est un (C_1-C_4)alcylène.

3. Procédé selon la revendication 2, dans lequel
R^3 est un (C_1-C_4)alkyle et
R^4 est un carbamoyloxy(C_1-C_4)alkyle; un hydroxy(C_1-C_4)alkyle; un hydroxy(C_1-C_4)alkyle ayant un amino ou un nitrophényl(C_1-C_4)-alcoxycarbonylamino; un difluoro(C_1-C_4)alkyle; un carbamoyl(C_1-C_4)-alkyle; un amino(C_1-C_4)alkyle; un N-[nitrophényl(C_1-C_4)alcoxycarbonylamino(C_1-C_4)alkyle; un (C_1-C_4)-alkylsulfonylamino(C_1-C_4)alkyle; un uréido(C_1-C_4)alkyle; un uréidocarbonyl(C_1-C_4)alkyle; un triazolyl(C_1-C_4)alkyle; un tétrazolyle, un pyrrolidinyle, un thiadiazolyle ou un tétrazolyle, où lesdits groupes hétérocycliques peuvent avoir un (C_1-C_4)alkyle, un N,N-di(C_1-C_4)alkylamino(C_1-C_4)alkyle ou un nitrophényl(C_1-C_4)alcoxycarbonyle; ou un (C_1-C_4)alkylsulfonyle.

4. Procédé selon la revendication 3, dans lequel
R^2un hydroxyéthyle,
R^3est un méthyle,
R^4 est un 2-hydroxyéthyle, un 2-carbamoyloxyéthyle, un 3-amino-2-hydroxypropyle, un difluorométhyle, un carbamoylméthyle, un 1-carbamoyl-1-méthyléthyle, un 2-aminoéthyle, un 2-amino-1,1-diméthyléthy-

le, un 2-(méthylsulfonylamino)éthyle, un 2-uréidoéthyle, un 1,1-diméthyl-2-uréidoéthyle, un uréidocarbonylméthyle, un 1,2,4-triazolylméthyle, un pyrrolidinyle, un thiadiazolyle, un 1-méthyl-1H-tétrazolyle, un 1-[2-(N,N-diméthylamino)éthyl]-1H-tétrazolyle, ou un méthylsulfonyle,
A est un méthylène, et
X est un soufre, un oxygène ou un imino.

5. Procédé selon la revendication 4 pour préparer le composé acide (4R,5S,6S)-3-[(2S,4S)-2-{(2-uréidoéthyl)thiométhyl}pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyéthyl]-4-méthyl-7-oxo-1-azabicylo[3.2.0]hept-2-ène-2-carboxylique.

6. Procédé selon la revendication 4, dans lequel
R^4 est un 2-hydroxyéthyle, un 2-carbamoyloxyéthyle, un carbamoylméthyle, un 1-carbamoyl-1-méthyléthyle, un 2-aminoéthyle ou un 2-(méthylsulfonylamino)éthyle et
X est un oxygène.

7. Procédé selon la revendication 6 pour préparer le composé acétate de l'acide (4R,5S,6S)-3-[(2S,4S)-2-(2-aminoéthyloxyméthyl)pyrrolidin-4-yl]-thio-6-[(1R)-1-hydroxyéthyl]-4-méthyl-7-oxo-1-azabicyclo[3.2.0]-hept-2-ène-2-carboxylique.

8. Procédé selon la revendication 4, dans lequel
R^4 est un 2-uréidoéthyle ou un méthylsulfonyle et
X est un imino.

9. Procédé selon la revendication 8 pour préparer le composé acide (4R,5S,6S)-6-[(1R)-1-hydroxyéthyl]-4-méthyl-7-oxo-3-[(2S,4S)-2-{(2-uréidoéthyl)aminométhyl}pyrrolidin-4-yl]thio-1-azabicyclo[3.2.0]hept--2-ène-2-caroxylique.

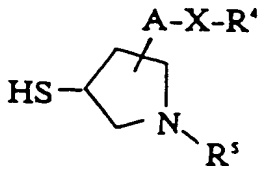
10. Procédé selon la revendication 2, dans lequel R^3 est un hydrogène.

11. Procédé selon la revendication 10, dans lequel
R^4 est un groupe hétéromonocyclique insaturé à 5 ou 6 éléments contenant de 1 à 4 atomes d'azote.

12. Procédé selon la revendication 11, dans lequel
R^2 est un 1-hydroxyéthyle,
R^4 est un pyridyle,
R^5 est un hydrogène,
A est un méthylène, et
X est un soufre.

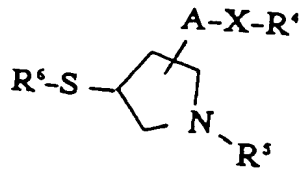
13. Procédé selon la revendication 12, pour préparer le composé acide (5R,6S)-6-[(1R)-1-hydroxyéthyl]-7-oxo-3-[(2S,4S)-2-(pyridin-4-ylthiométhyl)pyrrolidin-4-ylthio]-1-azabicyclo[3.2.0]hept-2-ène-2-carboxylique.

14. Procédé pour la préparation d'un composé de la formule :



(III)

dans laquelle R^4, R^5, A et X sont chacun comme défini ci-dessus ou les sels de celui-ci, qui comprend de soumettre un composé de la formule :

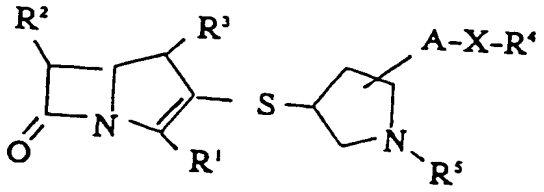


(IIIa)

dans laquelle R^4, R^5, A et X sont chacun comme défini ci-dessus et R^6 est un groupe mercapto-protecteur, ou les sels de celui-ci, à une réaction d'élimination du groupe mercapto-protecteur R^6.

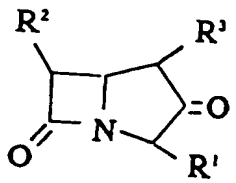
Revendications pour l'Etat contractant suivant : GR

1. Procédé pour préparer un composé de la formule :

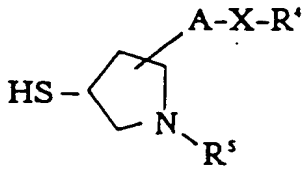


(I)

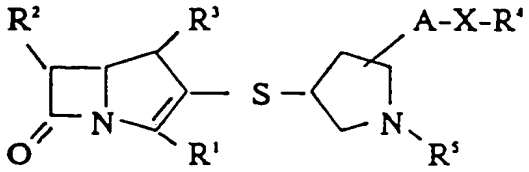
dans laquelle
R^1 est un carboxy ou un carboxy protégé,
R^2 est un hydroxy(C_1-C_4)alkyle ou un hydroxy(C_1-C_4)alkyle protégé,
R^3 est un hydrogène ou un (C_1-C_6)alkyle,
R^4 est un hydroxy(C_1-C_6)alkyle protégé ou non protégé; un hydroxy(C_1-C_6)alkyle protégé ou non protégé ayant un amino protégé ou non protégé; un halo(C_1-C_6)alkyle; un carbamoyl(C_1-C_6)alkyle protégé ou non protégé; un amino (C_1-C_6)alkyle protégé ou non protégé; un uréido(C_1-C_6)alkyle protégé ou non protégé; un uréiodocarbonyl(C_1-C_6)alkyle protégé ou non protégé; un triazolyl(C_1-C_6)alkyle; un groupe hétéromonocyclique saturé ou insaturé à 5 ou 6 éléments contenant 1 à 4 atomes d'azote ou contenant 1 à 2 atomes de soufre et 1 à 3 atomes d'azote, où ledit groupe hétérocyclique peut être substitué par un ou des substituants appropriés choisis parmi (C_1-C_6)alkyl, amino, amino(C_1-C_6)alkyle, mono- (ou di-) (C_1-C_6)alkylamino, mono- (ou di-) (C_1-C_6)alkylamino(C_1-C_6)alkyle et groupe imino-protecteur; ou un (C_1-C_6)alkylsulfonyle;
R^5 est un hydrogène, un (C_1-C_6)alcaneimidoyle ou un groupe imino-protecteur,
A est un (C_1-C_4)alcylène et
X est un soufre, un oxygène, un imino ou un imino protégé,
à condition que
lorsque X est un oxygène,
alors R^4 est un "uréido(C_1-C_6)alkyle protégé ou non protégé",
et les sels de celui-ci, qui comprend de :
(a) faire réagir un composé de la formule



dans laquelle R^1, R^2 et R^3 sont chacun comme défini ci-dessus, ou un dérivé réactif de celui-ci au groupe oxo, ou les sels celui-ci, avec un composé de la formule :

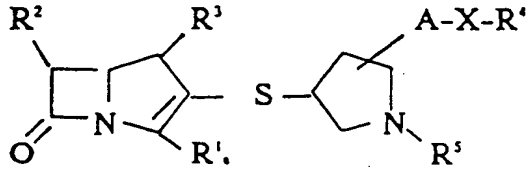


dans laquelle R^4, R^5, A et X sont chacun comme défini ci-dessus ou les sels de celui-ci, pour donner un composé de la formule :

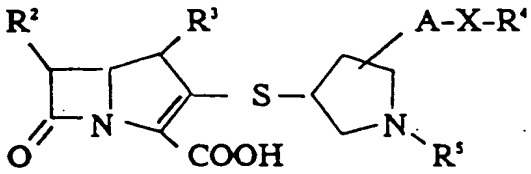


dans laquelle R^1, R^2, R^3, R^4, R^5, A et X sont chacun comme défini ci-dessus, ou les sels de celui-ci; et de

(b) soumettre un composé de la formule :

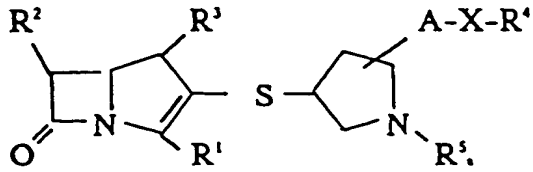


dans laquelle R^2, R^3, R^4, R^5, A et X sont chacun comme défini ci-dessus, et R^1_a est un carboxy protégé, ou les sels de celui-ci, à une réaction d'élimination du groupe carboxy-protecteur sur R^1_a pour donner un composé de la formule :

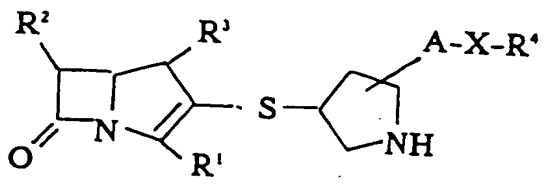


dans laquelle R^2, R^3, R^4, R^5, A et X sont chacun comme défini ci-dessus, ou les sels de celui-ci; et

(c) de soumettre un composé de la formule :

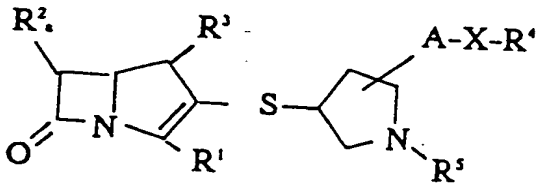


dans laquelle R^1, R^2, R^3, R^4, A et X sont chacun comme défini ci-dessus, et R^5_a est un groupe imino-protecteur, ou les sels de celui-ci, à une réaction d'élimination du groupe imino-protecteur de R^5_a pour donner un composé de la formule :

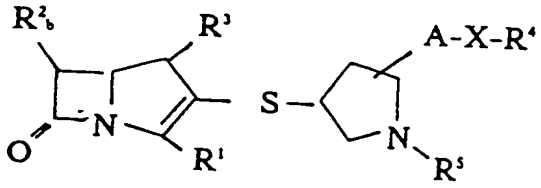


dans laquelle R^1, R^2, R^3, R^4, A et X sont chacun comme défini ci-dessus, ou les sels de celui-ci; et de

(d) soumettre un composé de la formule :

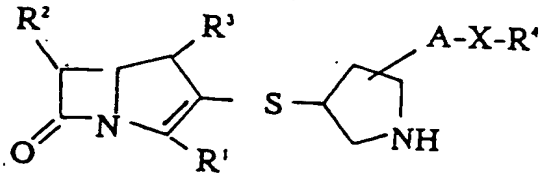


dans laquelle R^1, R^3, R^4, R^5, A et X sont chacun comme défini ci-dessus, et R^2_a est un groupe hydroxy(C_1-C_6)alkyle protégé, ou les sels de celui-ci, à une réaction d'élimination du groupe hydroxy-protecteur sur R^2_a pour donner un composé de la formule :

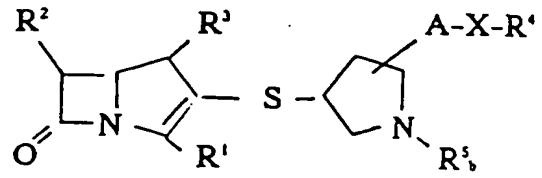


dans laquelle R^1, R^3, R^4, R^5, A et X sont chacun comme défini ci-dessus et R^2_b est un hydroxy(C_1-C_6)alkyle, ou les sels de celui-ci; et de

(e) faire réagir un composé de la formule :



dans laquelle R^1, R^2, R^3, R^4, A et X sont chacun comme défini ci-dessus ou les sels de celui-ci, avec un agent de (C_1-C_6)alcaneimidoylation pour donner un composé de la formule :



dans laquelle R^1, R^2, R^3, R^4, A et X sont chacun comme défini ci-dessus et R^5_b est un (C_1-C_6)-alcaneimidoyle ou les sels de celui-ci.

2. Procédé selon la revendication 1 pour préparer un composé de la formule (i) dans laquelle :
R^2 est un hydroxy(C_1-C_4)alkyle,
R^3 est un hydrogène ou un (C_1-C_4)alkyle,
R^4 est un carbamoyloxy(C_1-C_4)alkyle; un [phényl- (ou nitrophényl-) (C_1-C_4)alcoxy]carbonyloxy(C_1-C_4)-alkyle; un [triphényl(C_1-C_4)alcoxy](C_1-C_4)alkyle; un [tri(C_1-C_4)alkylsilyl]oxy(C_1-C_4)alkyle; un hydroxy(C_1-C_4)alkyle; un hydroxy(C_1-C_4)alkyle ayant un amino ou un phényl- (ou nitrophényl-)(C_1-C_4)-alcoxycarbonylamino; un dihalo(C_1-C_4)alkyle; un carbamoyl(C_1-C_4)alkyle; un trihalo(C_1-C_4)-alcanoylcarbamoyl(C_1-C_4)alkyle; un N-[bis{(C_1-C_4)alcoxyphényl}C_1-C_4)alkyl]carbamoyl(C_1-C_4)alkyle; un halosulfonylcarbamoyl(C_1-C_4)alkyle; un amino(C_1-C_4)alkyle; un N-[phényl (ou nitrophényl-)(C_1-C_4)-alcoxycarbonyl]amino(C_1-C_4)alkyle; un (C_1-C_4)alkylsulfonylamino(C_1-C_4)alkyle; un uréido(C_1-C_4)alkyle; un phényl(C_1-C_4)alkyluréido(C_1-C_4)alkyle; un uréidocarbonyl(C_1-C_4)alkyle; un phényl(C_1-C_4)-alkyluréidocarbonyl(C_1-C_4)alkyle; un triazolyl(C_1-C_4)alkyle; un groupe hétéromonocyclique saturé ou insaturé à 5 ou 6 éléments contenant 1 à 4 atomes d'azote ou contenant 1 à 2 atomes de soufre et 1 à 3 atomes d'azote, qui peut avoir un (C_1-C_4)alkyle, un N,N-di(C_1-C_4)alkylamino(C_1-C_4)alkyle ou un phényl- (ou un nitrophényl-) (C_1-C_4)alcoxycarbonyle; ou un (C_1-C_4)alkylsulfonyle;
R^5 est un hydrogène ou un (C_1-C_4)alcaneimidoyle, et
A est un (C_1-C_4)alcylène.

3. Procédé selon la revendication 2, dans lequel
R^3 est un (C_1-C_4)alkyle et
R^4 est un carbamoyloxy(C_1-C_4)alkyle; un hydroxy(C_1-C_4)alkyle; un hydroxy(C_1-C_4)alkyle ayant un amino ou un nitrophényl(C_1-C_4)-alcoxycarbonylamino; un difluoro(C_1-C_4)alkyle; un carbamoyl(C_1-C_4)-alkyle; un amino(C_1-C_4)alkyle; un N-[nitrophényl(C_1-C_4)alcoxycarbonylamino(C_1-C_4)alkyle; un (C_1-C_4)-alkylsulfonylamino(C_1-C_4)alkyle; un uréido(C_1-C_4)alkyle; un uréidocarbonyl(C_1-C_4)alkyle; un triazolyl(C_1-C_4)alkyle; un tétrazolyle, un pyrrolidinyle, un thiadiazolyle ou un tétrazolyle, où lesdits groupes hétérocycliques peuvent avoir un (C_1-C_4)alkyle, un N,N-di(C_1-C_4)alkylamino(C_1-C_4)alkyle ou un nitrophényl(C_1-C_4)alcoxycarbonyle; ou un (C_1-C_4)alkylsulfonyle.

4. Procédé selon la revendication 3, dans lequel
R^2un hydroxyéthyle,
R^3est un méthyle,
R^4 est un 2-hydroxyéthyle, un 2-carbamoyloxyéthyle, un 3-amino-2-hydroxypropyle, un difluorométhyle, un carbamoylméthyle, un 1-carbamoyl-1-méthyléthyle, un 2-aminoéthyle, un 2-amino-1,1-diméthyléthyle, un 2-(méthylsulfonylamino)éthyle, un 2-uréidoéthyle, un 1,1-diméthyl-2-uréidoéthyle, un uréidocarbonylméthyle, un 1,2,4-triazolylméthyle, un pyrrolidinyle, un thiadiazolyle, un 1-méthyl-1H-tétrazolyle, un 1-[2-(N,N-diméthylamino)éthyl]-1H-tétrazolyle, ou un méthylsulfonyle,
A est un méthylène, et
X est un soufre, un oxygène ou un imino.

5. Procédé selon la revendication 4 pour préparer le composé acide (4R,5S,6S)-3-[(2S,4S)-2-{(2-uréidoéthyl)thiométhyl}pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyéthyll-4-méthyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ène-2-carboxylique.

6. Procédé selon la revendication 4, dans lequel
R^4 est un 2-hydroxyéthyle, un 2-carbamoyloxyéthyle, un carbamoylméthyle, un 1-carbamoyl-1-méthyléthyle, un 2-aminoéthyle ou un 2-(méthylsulfonylamino)éthyle et

X est un oxygène.

7. Procédé selon la revendication 6 pour préparer le composé acétate de l'acide (4R,5S,6S)-3-[(2S,4S)-2-(aminoéthyloxyméthyl)pyrrolidin-4-yl]thio-6-[(1R)-1-hydroxyéthyl]-4-méthyl-7-oxo-1-azabicyclo[3.2.0]-hept-2-ène-2-carboxylique.

8. Procédé selon la revendication 4, dans lequel
R^4 est un 2-uréidoéthyle ou un méthylsulfonyle et
X est un imino.

9. Procédé selon la revendication 8 pour préparer le composé acide (4R,5S,6S)-6-[(1R)-1-hydroxyéthyl]-4-méthyl-7-oxo-3-[(2S,4S)-2-{(2-uréidoéthyl)aminométhyl}pyrrolidin-4-yl]thio-1-azabicyclo[3.2.0]hept--2-ène-2-carboxylique.

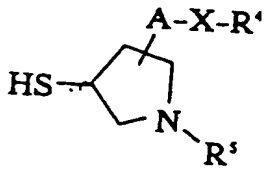
10. Procédé selon la revendication 2, dans lequel R^3 est un hydrogène.

11. Procédé selon la revendication 10, dans lequel
R^4 est un groupe hétéromonocyclique insaturé à 5 ou 6 éléments contenant de 1 à 4 atomes d'azote

12. Procédé selon la revendication 11, dans lequel
R^2 est un 1-hydroxyéthyle,
R^4 est un pyridyle,
R^5 est un hydrogène,
A est un méthylène, et
X est un soufre.

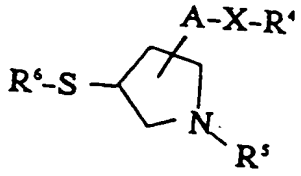
13. Procédé selon la revendication 12, pour préparer le composé acide (5R,6S)-6-[(1R)-1-hydroxyéthyl]-7-oxo-3-[(2S,4S)-2-(pyridin-4-ylthiométhyl)pyrrolidin-4-ylthio]-1-azabicyclo[3.2.0]hept-2-ène-2-carboxylique.

14. Procédé pour la préparation d'un composé de la formule :



(III)

dans laquelle R^4, R^5, A et X sont chacun comme défini ci-dessus ou les sels de celui-ci, qui comprend de soumettre un composé de la formule :



(IIIa)

dans laquelle R^4, R^5, A et X sont chacun comme défini ci-dessus et R^6 est un groupe mercapto-protecteur, ou les sels de celui-ci, à une réaction d'élimination du groupe mercapto-protecteur R^6.

15. Modification des procédés de l'une quelconque des revendications 1 à 13, caractérisée en ce qu'un composé préparé par un procédé selon l'une quelconque des revendications 1 à 13 est mis dans une forme acceptable sur le plan pharmaceutique par mélange ou présentation dudit composé avec un diluant ou un vecteur acceptable sur le plan pharmaceutique.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 87 11 7051

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
Y	EP-A-0 072 710 (SANKYO) * Claims *	1,11-16	C 07 D 487/04 C 07 D 207/12 A 61 K 31/40 // C 07 D 207/16 C 07 F 7/18 (C 07 D 487/04 C 07 D 209:00 C 07 D 205:00)
D,Y	EP-A-0 182 213 (SUMITOMO) * Claims *	1,11-16	
P,Y	EP-A-0 243 686 (SUMITOMO) * Claims *	1,11-16	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

C 07 D 487/00
C 07 D 207/00
A 61 K 31/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	22-02-1988	CHOULY J.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)